Meeting Minutes
Scientific and Medical Accountability Standards Working Group
December 1, 2005
Moscone Center South
10am-6pm

Attendance:

Working Group Members

Jose Cibelli
Alta Charo- by phone for select portions of the meeting
Kevin Eggan
Ann Kiessling
Bernard Lo (co-chair)
John Wagner-by phone for select portions of the meeting
Ted Peters
Francisco Prieto
Janet Rowley
Jeff Sheehy
Robert Taylor

CIRM

Zach Hall, Ph.D., CIRM president
James Harrison, CIRM counsel
Geoff Lomax, DrPH, senior officer for the standards working group
Kate Shreve, CIRM staff
Jennifer Rosaia, CIRM staff
Mary Maxon, PhD
Arlene Chiu, PhD
Nicole Pagano, office of communications

[Welcome, Bernie Lo]

[Roll Call]

Agenda item #4: approval of minutes from august 30, 2005

In the absence of a quorum, discussion of meeting minutes taken under advisement. No vote taken.

Agenda item #5: CIRM staff report

- Discussion of intellectual property task force recommendations
  - Presenters: Ed Penhoet, PhD; Jeff Sheehy
    [please see PowerPoint attached to this meeting agenda at www.CIRM.ca.gov "past meetings"
    [in the absence of a quorum, a formal vote was not be taken by the standards working group at this meeting regarding the IP task force recommendations. The sense of the committee was noted and communicated to the ICOC by CIRM president, Zach Hall.]
    Please see transcript pages 2-53 for Standards Working Group comments on the IP Task Force report at http://www.cirm.ca.gov/transcripts/pdf/2005/12-01-05.pdf. For additional information on the IP Task Force proceeding, please visit the CIRM website at http://www.cirm.ca.gov/transcripts/

Agenda item #6-review of draft language in the draft CIRM regulations

Informed consent

Bernie lo provided background to contextualize the crucial issue of informed consent

Today's goal: to come to agreement on a conceptual level [principles for informed consent] rather than wordsmith the draft regulations

There is a significant amount of existing law, regulations, guidelines with which all researchers, including stem cell researchers in California, are required to comply

Question: does this committee wish to incorporate any existing regulatory framework into its scientific, medical, and ethical regulations?

a. E.g., the federal common rule, ca state law provisions, NAS recommendations
b. Incorporation hinges upon what degree of detail is desired in these regulations

A. Issues:

1. Consent needs to be free or voluntary as well as informed.
    a. The common rile in California law really addresses what researchers need to disclosure to research participants in order to make sure that their consent is informed
    b. Concerns about undue influence with regard to oocyte donors is a reminder that consent needs to be voluntary as well as informed.
2. Recontact of donors of material for new stem cell lines.
    a. The NAS guidelines deal with [this issue] explicitly as do some of ca laws but in the context of providing information on research tests back to the participants in research [for the benefit of the donor].
    b. Do we also want to make clear to donors of materials that [researchers] may wish to recontact them, not necessarily for their benefit but to benefit potential transplant recipients of cell lines derived for their biological material? The goal of this recontact would be to gather more information about the donor's health status.
        i. [to gather more information or more material (Eggan)

3. Specific concerns regarding [the safety of] oocyte donation
    a. We want to put in heightened requirements for information consent for oocyte donors

B. Options for enhancing the informed consent process

1. Explicitly spelling out all requirements for obtaining informed consent
    a. This would lengthen the consent form
        i. Problem: all the empirical research we have supports the conclusion that longer consent forms are not the most effective.
2. Assessing comprehension
    a. If potential research subject does not demonstrate comprehension of the research, they may not participate in the research
    b. How to incorporate language of comprehension into regulatory language?
3. Third party interview-an independent person not part of the research team would observe discussions between the researchers and the potential research subject

a. This has been shown to have a salutary effect in terms of clarifying the discussion, helping the research subject ask questions.

4. Repetition
   a. Repeating discussions over time has been shown to enhance understanding.

**the Bedford protocol follows all of these approaches.

[response to the above framework presented by Bernie lo on the part of the other standards working group members present]

Cibelli: supportive of the "cooling off period" after potential donors have expressed a willingness to donate. Should also consider training the individual gaining informed consent. Could be conducted by the ESCROs. Could be an online training course that would need to be refreshed annually. In other words, have one designated trained/qualified person [on the research team] conduct the informed consent.

Eggan: as a scientist, I would argue for being as specific [in the body of the regulations] as possible for two reasons. 1) it will be clear [to the regulated institutions/scientists] how they are supposed to behave-and would thereby "level the playing field"—ensuring uniformity of expectations/behavior, 2) it will facilitate the research. E.g., having consensus regulations will help clarify best practices that will guide the research

Feit: a defined time-out in which there is no contact from the research team would give the [potential donor] time to get a clear understanding of the research materials that will allow for a full understanding of what they may enter in to. There should be a third party [unconnected to the research team] whom the potential donors may call for information, with whom they may feel comfortable. They would then verify that they had a "time-out" and an opportunity to really think [their participation] through. This time-out period needs to be clearly spelled. This is a very sensitive and high profile issue. It would help support [the goal of demonstrating comprehension] if the donors were given time to understand [what is involved with donating.]

Charo: are we talking about the best-practices universe of CIRM-funded research only? Or are we also talking about practices that we would require before we permitted a CIRM-funded researchers from using someone else's lines? Are we talking about what constitutes the minimum standard for an ethically derived line or requirements that govern recruitment of oocyte donors using CIRM funds?

Lo: good distinction—we will start by discussing CIRM-funded researchers and then address researchers deriving lines with other funds.

Rowley: point of clarification. It is clear that the regulations that that the individual donor is contacted by a physician or some individual not directly involved in the research so it isn't the researcher who's going to develop the cell lines who's is gaining consent [from the potential oocyte donor].

Taylor: agree that the waiting period is important along with counseling and ascertainment of understanding by the donor as well as the fact that consent must come from somebody other than the clinician who's caring for the patient clinically. There must be a "separation of church and state"—consent must be obtained by a trained independent individual and must require a waiting period.

Prieto: it is important to have a "time-out" but we also need to look into having a completely removed unaffiliated individual who would not be and would not be perceived to be [by the potential donor] part of the research team to whom the potential donor could turn for information.

Kiessling: the Bedford protocol provides a solution to the "cooling off" period by informing donors that no

one would contact them. Early in the recruitment when they were going through the initial screening, the potential donors themselves were responsible for contacting the office to make their next appointment. There are two big aspects of asking someone to donate eggs: 1) do they understand what might become of the cells derived from their eggs? Do they understand the biology? 2) do they understand the risks to themselves? It is possible to have, in this case, two different consent forms so that these issues get separated in the donor's mind.
Overall: what is the risk to self and loved ones (time commitment etc.,); what is the long-term outcome of donating? These are two very different issues and may require separate treatment.

Eggan: in agreement with [Kiessling]. A solution may be in leaving the recontact in the hands of the potential donor. It is important that the approach be sound in the sense of being impervious to criticism but also practicable. It is difficult to imagine whom the removed third-party would be who would be charged with obtaining consent. One approach-the research team could hire a dedicated research administrator for this purpose (e.g., a registered nurse). It is hard to imagine that this would be a functional approach for most research protocols (to "farm out" the consent process to an outside party.) It is important to recognize that many processes such as egg donation are multi-step, complicated processes. One way to handle this is to have a multi-step informed consent which is going to happen in the case of egg donation in the united states. Informed consent will need to be gained before a women goes under anesthesia for egg retrieval,

Taylor: a note about women or couples undergoing IVF and want to participate in a program like this. It may be a bit more difficult to be in compliance with a required time-out period in this context given that the IVF process is an intensive and relatively short period of time in which there is a lot of contact between the clinical office and the patient. Thus this requirement may exclude couple undergoing IVF for their own clinical fertility reasons who may want to participate. Including language that limits the allowable contact between the participant and clinician's office may be limiting—I see that as being the most prevalent mechanism for obtaining these materials and wouldn't want to write it off up front.

Kiessling: it is more important for the patients going through infertility treatment to have the opportunity to have a time out. There are a lot of pressures on those couples, and for them to participate in research it is even more critical that they have time to reflect on whether they want to [participate in research] in addition to their infertility needs. It is more critical in this group of women that in the group of women donating because they have type 1 diabetes in their families.

Rowley: this was addressed in the NAS report—anyone who is giving embryos no longer needed for their own family building have to be reconsented in order for those embryos to be used for research. So they have up to years as a "time-out".

Lo: to clarify, we need to be very careful to distinguish the donation of frozen embryos remaining after infertility treatment is completed from donation of fresh oocytes. [Taylor's] comments were related to the donation of fresh oocytes from a cycle where they are also donating for infertility treatment.

Taylor; I was thinking of the frozen oocyte donation model because most couples don't really know what the outcome is of their pregnancy cycle until after the fact. If you required a waiting period that couples undergoing IVF couldn't really accommodate in their intense [treatment] cycle, it would be nice if they still had the opportunity to participate and be required to reconsent at the time of donation. This could be called the time-out.

Lo: my understanding is that the NAS report built in that timing after the oocytes are in the freezer. This would be the literal "cooling off period."

Eggan: we should be careful about terminology-embryo versus oocyte. There are circumstances which are not directly addressed by the NAS guidelines. E.g., in which a couple undergoing IVF where there will be discarded material that may be used for research. It is still an ongoing discussion whether or not we should support the sort of diversion of material generated fore an active attempt at pregnancy toward research—but there may be some instances where it is useful and in which there is no question. For instance NAS guidelines directly encourages freezing of donated embryos—but there might be other embryos such as those affected by a variety of diseases that have been diagnosed by PGD which would be ed facto discarded, which could be used for research. In cases like this in which the material would be otherwise discarded. To mandate a cooling off period could be difficult in this situation.

Lo: would you include oocyte that fail to fertilize?

Eggan: that is something about which we should have a broad conversation. That is a troubled source of material for a variety of reasons. Others disagree. HFEA has endorsed that.

Lo: let's focus on the normal situations, not the unusual ones.

Feit: if I am donating ant part of my body and you say I'm going to freeze it for five years or longer—I don't have to worry about it. Then if you come back to me and ask permission to do something else with my materials, then I deserve time to think about the implication of that decision. That is how patients and donors think. Don't underestimate that, because they have 5 years [between depositing the material into a cryopreservation bank and being faced with a decision of whether or not to donate the material to research] that they clearly understand the implication of (donating for research). The moral ethical duty we have is to make sure that participants understand [what is involved in this decision

Lo: there is no time constraint on this period of reflection because the material is frozen. This would be a departure from the way that consent to donate frozen embryos for research purposes is currently done. Much of the time it is actually coupled with the bill you get for the storage fees. If you don't want to pay and you don't want to keep [the embryo(s)] frozen, one option is to donate them to research. This kind of discussion is not necessary had.

Eggan: this may be a similar situation—if it is sent out without direct patient interaction with the bill, and they receive the bill and the document in the mail, they can decide to wait as long as they want to wait before they recontact the IVF clinician. So there is a de facto time-out or "cooling off" period. There is no direct coercion or encouragement to donate embryos. The decision is up to the individual/couple—the could just as easily not pay the bill and decide to discard the embryos.

Taylor: we are talking about a staged consent process and I don't want for us to miss the first stage. Anybody for whom embryos are going to be frozen and stored potentially for research are going to have to go through the initial consenting process. I want to make sure that there's going to be enough time as well as a good mechanism built in for that to occur. We don't want to have the only embryos that we would ultimately have access to be clinically frozen embryos that the couple has decided not to use—this would be going back after the barn door is closed. We want to have consent up front at some level—not final consent, but some level of informed, comprehended consent.

Prieto: agree. In any institution that is considering that sort of use of embryos downstream, some initial consent should involve the basic statements to make clear to the individual/couple that one consideration down the road may be the use of embryos for research-that they should be aware of that and think about it without this being the final step.

Eggan: or, more explicitly, there could be a check box with which someone could indicate having a

disposition donating discarded embryos or other material for research. Those that indicate this disposition would then be provided with pertinent information.

Taylor: that is how a lot of places are doing it.

Rowley: two issues.. One, there are now reports of using materials other than oocytes for SCNT/ that is not dealt with in the guidelines right now at all. If, in fact, some of these other techniques become more widely used, then you can say that oocyte donation is almost a moot point. Two, it is impossible to explain to the patient what's going to be done with these embryos and the resultant cell lines because no one knows what the research landscape is going to look like in the future and what an investigator might do with a cell line in the future. Giving the patient the option of opting out of [having their material used for] certain types of research is not a practical approach. I urge that we not include that in the guidelines.

Eggan: there is a brief statement in the NAS guidelines encouraging scientist to pursue alternatives to the use of oocytes in creating patient-specific or genetically tailored stem cell lines—I think that it's important for us to transpose that type of material into our guidelines. I also think it's important to point out that these technologies for the time being are far from replacing the techniques hat we know can work and that have been developed in south Korean and that were used to clone dolly. For the time being, the only functional means that we have of making tailored cell lines is through SCNT and donated oocytes. Again, the only methodology which has worked is somatic cell nuclear transplantation into oocytes directly and specifically donated for research. Attempts to do hat will failed-to-fertilize oocytes have not yet been successful. For the time being, if this is a priority, we need to put the ethical safeguards in place to make sure that the research can go forward as we know that it can work. As far as opting out, I tend to agree with [Rowley]. This would make downstream use of any individual cell line extremely difficult. We would hope that enough people would step forward the a broad consent that it might be simplest to use only resources from those donors to move forward.

Kiessling: based on this discussion, it seems that it's going to be more fruitful to focus on the types of things being donated in terms of consent. For instance, why don't we just discuss informed consent for women donating eggs? And then discuss informed consent for couples deciding to donate left-over embryos. Because of the circumstances, these really are two different processes.

Prieto: it would be difficult to parse out every potential downstream use of materials. I think a broad general consent is what we want to ask people for that might include some mention of some of the potential uses such as those mentioned in the NAS guidelines (with the understanding that this would not be a comprehensive list.) The consent forms should not give people multiple options of agreeing to some uses and not others as well as fail to address techniques hat may exist years from now.

Lo: so you would like to see a consent form that indicates a participants consent to donate material with the understanding that it will be used in the future for stem cell research including research that may or may not be conceived of at present, as long as it's approved by an IRB/ESCRO. This consent form would not include the option opting out of research such as injecting cell lines derived from the participant's material into nonhuman blastocysts? Are you saying that we would like to have a donation of oocytes for any purpose in the future for research that is approved by an ESCRO and has scientific validity?

Eggan: the oocytes are going to be donated for the use of deriving stem cell lines, and those stem cell lines should be able to be used for molecular, cellular, and developmental biology in the broadest sense.

Hall: as well as for therapeutic purposes.

Taylor: if we had a two-staged consent process, the first being fairly general and the second state would

address more specific uses of the cells. This is something that we discussed in san Francisco a couple of years back, that there are going to be donors who are very interested in donating materials to understand early human embryology but don't want to see a propagated cell line with their genetic material. The opportunity to opt out of specific things should be one of the rights that a donor has. We might consider a two-staged process that allows for this.

Eggan: it seems like those are different studies which might involve different types of consent. Would there be cell lines derived under certain circumstances which will only be used for certain purposes? That possible, but then there needs to be some type of asterisk placed by those lines. How will this be done in the future? That may be something which falls on the investigator themselves as far as distribution of those lines into any particular bank. Different types of research purposes then may call for different consent processes.
Research to derive cell lines would be a totally difference consent process than that derivation of lines intended for broad distribution.

Feit: how will you track that? If I am a donor—how are you going to track my donation though all of that. I think it would be very difficult. You first statement about keeping the consent broad but qualifying that biomaterials may be used in certain ways and that any time my donation will be used in approved research validated by these organization and only that type of research—I have a comfort level that I've done the right thing. But you have to ask yourself how are we going to track an individual's request for how their materials may or may not be used through all of the different opportunities that might occur as a result of the donation.

Eggan: I can think of one specific example to draw a broader line between two different consent processes. One person might be comfortable with donating their embryos for the derivation of stem cell lines which will be propagated over a long period of time and could help many different scientists. Another study might be to take human preimplantation embryos and do some experimental study on those embryos themselves to better understand the embryo which could help in deriving stem cell lines. That is an embryological experiment-it doesn't result in the generation of a stem cell lines itself and in the process of doing the experiment, the embryo is destroyed. This would be an entirely different sort of consent process. People who would consent to the first experiment might not consent to the second.

Taylor: you capture both groups.

Eggan: I don't know if one can capture both group up front.

Lo: if you're going to ask fro a donation to derive a new hES line, the donor must understand that those sc lines could be used for a lot of different purposes, some of which we may not be able to predict, but will be overseen by the ESCRO mechanism. If you are not comfortable with that , there's still another option to donate embryos for scientific project that do not involve the creation of a sc line but may involve genetic developmental research. Because we don't expect those cells to be propagated in a lab, we should be able to say what they will be used for in a much more closed-ended way, but that would be different types of research. Does that capture the concern?

Taylor: that sounds good. For Marcy, I think that the tracking mechanism of how these sc lines are going to be used—I see this as falling to the ESCRO. I think it's going to be actually one of the important responsibilities of the ESCRO, not only to maintain a running list of the kinds of cells that you have in your system but also to be sure that the things that they're consented for are where they're actually going.

Eggan: the real responsibility lies with the investigator and there should be oversight by the ESCRO.

Lo: we need for this to eventually tie to the banking issue. If we are depositing materials, including sc lines in banks, then presumably I'm hearing that we don't want the bank to have to try and keep track of how the cell lines is used in compliance with what the donor consented they be used for.

Rowley: it is possible for bank to actually say that they will only accept cell lines that have a broad consent form for use in many difference experiments, including those that we envision at the present time? I think this will be too complicated and unenforceable. We have to avoid that because we do not know what the future will be. To have to revise the regulations every time some new nuance comes forward is a mistake.

Lo: this sounds like a key element. You want to make sure that people understand when they donate that there are a lot of [research] purposes that we cannot anticipate and you have to feel comfortable that scientists and the oversight bodies will be responsible in only allowing research that scientifically meritorious and ethically acceptable.

Taylor: the recontact issue in this particular field is absolutely critical. We really don't know what the future is and we do need mechanism to get back to individuals and find out both health information about the donors as well as consenting kinds of issues, particular as we go forward. I can envision that there would be people who don't want to be recontacted and do want to donate and there can be some specific endpoints there , but I would hope that those donors that are willing to be recontacted will form a subset of samples that can then be used in more innovative ways.

Lo: can someone help me understand the psychology of donors? How likely is it that someone who decides to donate for this future research would say I don't want to recontacted to give further information that you tell me might be useful to assure the safety of the use of transplantation of cell lines derived from my biomaterial.. If we follow the principle that we would like to have cell lines that are unrestricted in terms of donor preferences because it would give you the most flexibility to carry out different types of research, would we be losing a lot of cell lines of those donors who might uncomfortable with being recontacted?

Feit: having worked with organ donors a lot, I can tell you that it's very gratifying, it's a very stressful decision and it's usually tragic to make a donation. Once it's done, many times they get a wonderful letter or call from the network telling them what happened. It's very rewarding to know that something very positive came out of a situation. In terms of thinking generally about people who make these decisions is that we can make an assumption here that the research we're looking forward to is going to have some very positive things happen, therapies, cures, and changes in how we approach disease. Having a recontact is a very supportive thing to encourage. It's been my impression that if they agree to be contact that's a very positive thing.

Eggan: in the case of organ donation, that makes a lot of sense—in many cases it is an independent decision to do something philanthropic . At least with donation of discarded embryos after IVF, I think it's important to note that, although disassociated from the original process of IVF, for many couples it's reasonable to say that it may be the most difficult time in their lives, the process of undergoing assisted reproduction. At least IVF clinicians that I've talked to fell very uncomfortable about recontacting patients and clients who have undergone that process. Certainly some types of donors it would be appropriate to recontact. For other I things we should be more careful as to what that is going to mean to them to dredge that period of their life up again.

Kiessling: this would be more constructive to separate out what we're talking about. I think recontacting a woman who comes forward to donate her eggs for stem cell research is a very different process from

recontacting couples who have gone through IVF. We want to separate out what it is we're consenting to or who's consenting to what. These things are being lumped together.

Lo: let's stay focused on the oocyte donors which are the most complex and controversial.

Cibelli; you're mixing donation of frozen embryos with eggs or with gametes for the purposes of SCNT. We are going to have different consent forms for different things.

Taylor if we're going to pick oocyte donation as the one to start with, it should be further separated from donors who are contributing oocytes to an IVF cycle versus those who are donating to a scientific protocol.

Lo: why don't we start with donation expressly for the purpose of research. This would be similar what [Ann Kiessling's group] is set up to do. To review some of the things that have been discussed:

- We would want a time-out period
- We would want some assessment of comprehension
- Consent should not include lists of types of possible research uses-this will be difficult given that we don't know what the future of this research will look like
- There would be the possibility of recontact

Do we want a cooling off or time-out period for oocyte donation? This seems fairly easy to build in because it's an elective cycle.

Taylor: a time out period would be appropriate. It addresses if not removes the coercion factor from clinical care.

Lo: objections to a time-out period?

[no objections voiced]

Do we want the person obtaining consent to ascertain comprehension of what was disclosed?

Eggan: it is hard to do that—what would the mechanism be to assess comprehension? The process of informed consent is tricky.

Kiessling: it is really important. As I mentioned earlier, it has to be broken into pieces. She has to understand what the risks are to her which is most critically important—that she's been read what the risks are and that she really understands that this is not without risk and that she's assuming these risks of her own free will. And then I think she needs to understand the science of what might happen. I think those two pieces can be pretty easily assessed.

Lo: one option is to have a series of questions that need to be answered appropriately by the potential participant in order for him/her to be able to participate.
researchers obtaining informed consent of oocytes solely for research must ascertain that the donors understand the essential features of research. Research may meet this requirement by following a process that is approved by the relevant IRB or ESCRO. The essential features that must be understood shall include :

1) Embryos will be created for research which will not be used for reproductive purposes
2) There are medical risks in oocyte donation-we need to think how detailed the information should be in defining the risks-for example, should it say that there may be a risk of OHSS
3) The research will not benefit donors or any other individuals directly at this time
4) Stem cell lines developed from their oocytes will be grown in the lab and shared with other

researchers. Need to add range of purposes some of which we cannot predict
5) The stem cell lines may be patented, but donors will not share in the any revenue
6) Donors receive no payment except reimbursement for out-of-pocket expenses
7) If stem cell are transplanted into patient, researchers may want to contact you to get more information about your health
8) Potential donors are free to decline to donate oocytes for research without any negative impact on their clinical care.

Eggan; I'm not worried about what's good or not good, but how do you administer this test? Is it a written test, do they have to get a hundred percent correct? If not are they retested? What is the mechanism?

Feit: we do this all the time. We assess an individual's knowledge or understanding of a procedure. We do major surgeries and we expose them to a lot of information about the risk of anesthesia etc, both pre and post-operative risks. There are ways to do that.

Eggan: as a researcher, I want to know, what is the mechanism? When I'm building my research study and this is an important aspect of the research protocol, what is the mechanism? Is it a conversation? Is it some kind of test that can be scored which I can hand to my IRB which says objectively that this person understands? I agree that this is important and want to understand how we do it.

Feit: I would have one of our research nurses develop an interactive module which puts the donor privately though and assesses whether the donor really understands the information we gave them. Definitions-making sure that the donor really understands the information we gave them and then just putting them back through the questions. It can be done in an interactive module in which the donor provides yes and no answers of whether they understand.

Eggan: it is one thing to say that one understands but this may not actually be the case—this is the complicating factor that I'm trying to get to the bottom of. Signing at the bottom of the consent form says that they understand, right? So it's not really any different.

Kiessling: the person that we found to do this for us is an attorney who is also a nurse who also went through infertility treatment and she talks to the donors one on one and simply asks them questions. Do you understand the risks? And then [the interviewer] provides a report. It's also possible to draw up a paper test that would also satisfy that. This is very complicated. We haven't drawn up a paper test because we've been very satisfied that this independent person who gets to talk to the donor in private is trained to understand if this person is really comfortable with what they are doing. A big sideline concern about this is that this donor is doing this free of coercion from anyone in her family. So this independent monitor is able to figure out does she understand what she's been told? And this is frequently 2-3 months after she initially read the consent form. This is not 2-3 days. It takes months to get through the screening process. So if she still understands it, if she remembers it, if she knows the risks, the monitor can figure that out pretty comfortably. You could also define a set of questions that you would like asked and the answers that you expect, but this is really not hard to do.

Lo: we should try to distinguish between regulations and best practices. Kevin, you're going to want to do this really well and put a fair amount of effort , get some collaborators who are psychologists. I think you and Ann and groups like you should publish how you do it as a model, as a template. In regulation, I'm not sure we want to be too prescriptive at this point. Ultimately it is up to your IRB or ESCRO to approve the protocol. But to give a lot of flexibility to allow different investigative teams to figure out how best to do this. It think there are clearly models from the transplant setting here where, for example, people who do live donation of liver segments and kidneys go through this very complicated process where all of these issues get talked about in detail. The other extreme in aids clinical trials in developing countries where

there is a lot of concern that people don't understand that it's research and not clinical care and that they can still get aids even though they are getting a vaccine. It's a paper and pencil questionnaire which may be too basic for these purposes.

Rowley: there has been the suggestion this be uniformly done across California institutions.

Lo: absolutely, thank you.

Cibelli: going back to the consent form-we're talking about donating eggs exclusively-how much detail on what your intentions are for the eggs are you going to provide in the consent form? You can destroy them immediately and do proteomic analysis or you could do nuclear transfer, produce a cell line, and it would be used for many years. So what level of detail will be provided in the consent form [regarding outcome or intention for research purpose]?

Lo : I thought we were talking primarily in terms of deriving a stem cell line from their eggs, but you are right—other researchers may want to do something that does not involve a stem cell line creation.

Cibelli: we can create a line by fertilization, nucleate transfer, and parthenogenesis—

Lo: those are issues that certainly the IRB needs to deal with. The question is do we want to be that specific in the regulations? That's a policy choice we need to make.

Cibelli: what are the rights of the donor? Isn't she entitle to know? Or is it just entrusted to the ESCRO that they are going to do the right thing.

Eggan; I would think that it is not enough to ask a woman to donate her eggs for stem cell research in general. And the proximal event should be well prescribed in the consent. E.g., we are asking you to donate your eggs for an somatic cell nuclear transplantation to make a cell lines which will be broadly used or we're asking you to donate your eggs for parthenogenesis—perhaps in the same consent form.—the goal in each is the same, to derive a cell line that will be used broadly. But then it seems a different thing to donate your egg which then may be destroyed for an experiment and a new cell lines will be made.

Hall: DNA contribution is different for one thing.

Lo: if you are dealing with fresh oocytes, you know what you are doing with it, right? Thee are only several experiments you are likely to do at that point because you have to be set up to use the oocyte immediately.

Taylor: IRBs require a certain level of explanation about the protocol. I don't think this process is going to move beyond an existing expectation that donors are going to have a pretty clear idea about what the experimental protocol involving their materials is going to include.

Cibelli: are you saying we don't need to worry about it?

Taylor: your IRB is going to make [the investigator] worry about it—[the investigator] is not going to have the opportunity just to take someone's eggs and do whatever he/she wants with them.

Cibelli: what I am asking is whether [this committee] does not have to worry about talking about [this degree of detail]?

Lo: that is a choice that we need to make or we may want to say that you need to include, for example, whether or not research using donor materials will be somatic cell nuclear transfer rather than parthenogenesis.

Cibelli: does California law include any statement about donation of gametes

Lomax: the existing law include statements about intended use but there are no statements about prohibition in the law (from which the CIRM is currently statutorily exempted) but the intent of that law is to provide knowledge about the intended use of the material t hat is being donated.

Cibelli: what if we want to make stem cells from a day 21 embryo that has to be put in the uterus and somehow flush it out to get cells?

Lo/Rowley: prop 71 prohibits growth beyond 12 days.

Cibelli: that takes care of that-that is not a problem. Ann asked the question of me—can you fertilize this gamete and produce embryonic stem cells from it or do you have to use just embryos [that have been fertilized—to get a cell line that is the product of fertilization—can you get it from an egg that someone donated—[and fertilize the egg?]

Lomax: yes

Eggan: only in the state of Massachusetts is that expressly prohibited. There are other states where everything is [prohibited]. Massachusetts is the only state that would allow you to derive from discarded IVF embryos or other IVF embryos but not specifically allow you to mix oocyte and sperm in a dish for the purpose of stem cell research.

Lo: to be clear, we are talking about incorporating existing California law even though we are not required to under prop 71 into our regulations. We've reproduced the relevant law that has to do with donation of gametes, embryos, and somatic cells for cell lines. Existing law does not exclude certain types of things but it specifies certain things that must be told to prospective donors. By incorporating that into our regulations which will need to be disclosed to donors donating oocytes solely for research. [see health and safety code 125315]

Prieto: I thought I was hearing from Kevin earlier that he feels that most scientists would prefer that requirements be clearly laid out so that expectations were clear from the beginning. The advantage of referencing [existing law] is that it is already laid out there but I don't think that addressed some of the specific issues with regards to stem cell research that are addressed. I think we would want to add that because there are certainly unique features of this research that are addressed in the NAS guidelines but are not in California law now.

Lo: one proposal is for us to incorporate not just these California laws but also the NAS recommendations. We would need to think about how to do this technically, but that would also be incorporated as requirements that research must disclose in the process of obtaining informed consent.

Prieto: I would favor that—it would give us the advantage of being consistent with existing California law.

Lo: these are all things that currently stem cell researchers in California are subject to.

Wagner: you've changed direction a number of times for a number of good reasons. From a practical point of view, when I 'm working with an IVF center, I'm not involved with oocyte donations. There will be

PGD in an IVF clinic. There are some practical issues that need to be overcome. Typically families or couples will come in—if they are going through IVF for the purpose of infertility—those "excess" embryos are then stored and they are not reconnected with anyone for years. Somewhere down the line, someone contacts us from the IVF center and says here's a couple who may be interested. The issue of recontact is a difficult issue. The IVF centers are not part of the research team, at least the ones I have dealt with—they want to play a role but on the other hand, they are not very involved. So we can only ask so much of them. I can come up with ideas on how we might be able to get a more balanced or better consent process [in the context of the IVF center] or else provide the consenter. IVF center staff generally know a cursory amount about ES lines and what they might be used for but they are not the optimal people to provide that consent for us. Yet, as a researcher I may be 2,000 miles away from [the IVF center providing the embryos] which limits the ability of the researcher to be hands-on. Regarding recontact—the IVF center who are the primary point people don't want to do that a lot of the time anyway. Even when it comes to the idea of recontact for the purposes of health screening, remember that we're dealing with adult couples. So health screening should be done as part of the entire procedure up front rather than at the point after having created the sc line—I don't want to find out at this point that the cell line is problematic--this is an inefficient process.—I would want to know this information up front. You want to have clear way of connecting [with a donor] if you really had t—think also about the cord blood banking process that's been publicized In the recent past. We don't go back for them in the majority of cases, if ever. If you're planning to [establish a mechanism for recontact] up front—great—just be prepared for the event in which you are not able to recontact [the donor]. Do you not use that cell line? Do I really want to invest in making an ES cell line [keep in mind the labor and inefficiency of creating a cell line] to then find out that I cannot use the lines or explore another area of research with the ES cells because I was not able to recontact the donor. Keep in mind that [recontact] is not very practical to do. I'm not sure that we really need to do it although maybe in the argument today, we might have given response why we should and I couldn't hear them [Wagner is participating by phone over a faulty connection]
I agree with you that IVF should be separated from the egg donation but IVF is not always the same. Infertility and PGD are very different and there are reasons why, with PGD you might want to use fresh embryos and, therefore, if you're going to have to consider the consent early on. This is a decision that can be discussed well in advance of the actual IVF procedure if you really wanted to because these are people that are going into this, not for infertility, but for other reasons. I agree with whole concept of having plenty of time to get consent and having time to think about and ask questions. I get consent every day for a life threatening procedure call bone marrow transplant and we certainly know how to get consents for such tricky things as transplants. I think we can come up with ways, for example of how you do this so that the investigator, who really is the expert is ES cells, not the IVF team, certainly can do that by creating a video. There are things that you can do that make it less coercive and as objective as possible even in terms of trying to assess comprehension—a process which is simply to ask a number of key questions. In this particular case you are going to have to find a way to address questions that the IVF team might not necessarily know how to address. The elements that have been discussed are important but sometimes what I'm hearing is something that isn't going to be easily out into practice. I'm not really sure what you gain from this in the end.

Charo: I would like to endorse the notion of practicality. Bernie may remember, we went around on this question about donor control of tissue uses in the Clinton bioethics commission. We found that there was a genuine disagreement about whether it was realistic for people to consent prospectively to an unknown range of research facilities, come of which weren't even conceivable at the time of donation. The majority of us felt that this is a choice that people ought to be able to make, especially when we have asked for protection for their own confidentiality down the line because the problem with tracing each lines back to its original set of conditions is tremendous and makes it so much harder for the lines to be shared around. I would like to urge that we keep out eye on facilitating the research as much as on making sure that as a substantive and political matter we pay attention to the ethics of the donations.

[lunch recess]

[public comment]

Reed: recommendation that the SWG communicate with the legislature regarding the proposed regulations and the issue of revenue stream to the state. Re: egg donation-the UK program teaches a course and every potential egg donor must pass a test to be eligible to donate. Does not consider that an exhaustive description of possible uses is warranted in consent if donor consents to donate for research purposes—suggests that once research has been made clear and all of the possible uses have been explained informed consent should include question, "would you like to help possibly save lives and alleviate suffering with the precious gift of oocytes?". Advises educating donor thoroughly, assessing comprehension.

[lo provides summary of the morning session to assess agreement on some of the broad issues related to oocyte donation specifically for research, not for fertility purposes.]

A. Should there be a time-out? Reflection, question/answer period before a donor is asked to make a final decision?
B. Assessment of comprehension of crucial features of informed consent—the science of how materials will be used and the medical risks to the donor
    a. Ann mentioned that one of the things her donors are interested in is what is going to happen to the oocytes in the lab. She mentioned that many women are willing to have their oocytes used for SCNT or for parthenogenesis but not to fertilization to produce an embryonic stem cell line.

I thought I heard agreement on the fact that we didn't want donors to impose restriction on specific subsequent downstream research use of oocytes. This would be with the understanding that it would pass ESCRO approval and remain within the statutory restrictions established by prop 71 including 12 day restriction, no breeding of human-animal chimeras. Is there broad agreement to put into regulatory language this notion of a time-out period. Any concerns or objections?

[no objections to a]

Some assessment of the crucial features of the science and the risks, including the immediate use to which the oocytes are being used.

Taylor: include a point for the addressing the donor's own health risks.

Prieto: isn't that under "risks of participation" –isn't this addressing the medical risks to the donor?

Lo: we need to include the notion of how uniform or proscriptive we should be about how the assessment is done. On the one hand, there was a sentiment that there be uniform requirements so that one site is not considered to have weaker/stronger requirements than any other. On the other hand there is the idea that we may want to allow flexibility for different investigative institutions to test different models—to establish best practice guidelines. Do we want to be prescriptive not only in terms of the issues that are addressed but how they are going to be evaluated.

Cibelli: question for Marcy. Do you think that the person that actually will ask the donor to sign the consent form, in this case a research nurse, do they have to go through some training just for this particular exercise, or is it something that we can given them a form and read it and they will be qualified enough to administer the consent form and get voluntary and informed consent.

Feit: I know that the research nurses I've worked with are extensive trained in what they're doing. They have to understand what they're asking. They have to fully understand everything.

Cibelli: do they go through a training period?

Feit: yes

Lo: do you want included in the regulations the requirement that the person obtaining consent has to have adequate training, and we say leave it up to the IRB to ensure [compliance with training requirement]

Cibelli: it doesn't have to be a burden that is going to limit the research and make things more bureaucratic. In my institution, Michigan state, if I'm working biosafety level II, I have to be trained every year. Maybe the first time, it takes 3-4 hours and then every year on the web I have to doa refreshment course that takes ~15 minutes. My recommendation would be that the person that is going to interview the donor has to be trained in how to do it because in the end, as Kevin was saying, when you signed the informed consent, you're saying that you understood everything. Well, do you really understand it or not?

Taylor: the IRB's allow this to happen in a number of different ways. This might be an ESCRO responsibility because, particularly if we are talking for a relatively uniform procedure across the various centers, I think the ESCROs would probably approve or follow the qualification of this consent obtaining individual. The way that IRBs do it now in most institutions is that the pi of the project verifies that there is an appropriate person to obtain informed consent, but we could add another layer of supervision. It probably isn't the IRB's responsibility to do that. They don't have this responsibility for other protocols so it seems to be more of an ESCRO responsibility.

Feit: Wouldn't it be better for us to have a more global position and say that we will require that a thorough assessment be made of the patients' understanding of the condition and the expectations of the donation, and then have available a best practice program for people to look at which outlines what we expect? Institutions would not be required to adopt it identically given that each institution has its nuances, but we could certainly establish a best practices guidance.

Eggan: I agree with Marcy. Another way that one can help safeguard against coercion and lack of clarity and understanding on the part of the donor is to have a safeguard where any member of the research team, be it the research nurse who's consenting to a clinician directly involved with retrieval, can veto the participation of a potential donor whom he/she believes, for whatever reason, is an inappropriate donor. The word of a single members of the research team should be enough to disqualify a potential donor from participation.

Prieto: That is setting a pretty high bar.

Kiessling: That's actually how we do it. If anyone on the team has questions, the [consent] document doesn't go through. I don't know that you want to put that in regulation.

Hall: You could require the approval of all of the people who have had contact with the potential donor.

Eggan: This would be a more positive approach

Feit. That could be put in best practice guidelines. I think if we have in our regulations that we say definitely there has to be proof of a thorough assessment of the patients' understanding and willingness

to move forward with donation, and then we have available a best practice model that incorporates the standards that have been talked about.

Lo: this may cause problems with administrative law office [staff note: we are limited in our ability to establish best practices guidelines outside of the regulations—these could be interpreted by the office of administrative law as an underground regulations.] We will need to consult with consult with legal counsel and staff as to whether it is possible.

Eggan: I don't know if Marcy is willing, but that is something I'm happy to work with her offline on.

Lo: Marcy, Ann, and Kevin could come up with [language] that would be useful—this does give us a chance to forge new territory.

Cibelli: I do want to address the public comment on the fact that the UK has a course for donors. I think it's a great idea, but the problem would be to be able to maintain confidentiality of who actually is attending this class. This is the drawback.

Kiessling: One of the things that we might have to consider is that we send some time with the donors actually for them to understand why it has been decided that they can't participate because this can become very personal. We spend some time explaining to them that there is a whole variety of reasons that they may not be allowed to move forward. This is included among the category of understanding the risks to participation.

Lo: We said we were going to limit the discussion to donation of oocytes specifically for research—there is a complementary issue of women who are also donating for a woman in an infertility practice other than themselves. What about the issue of they're also donating some oocytes for research purposes? There are two issues-1) it's not just a consent issue. Some of it is how do we change the consent. 2) is this [donor scenario] something we would approve of? Encourage? Discourage? It's a complicated issue.

Taylor: A couple of the issues of interest here are that women who are recruited for oocyte donation for IVF programs tend to be young women from whom we can get a large number of eggs, oftentimes many more than what are need for the IVF procedure itself because the eggs are from young—typically fertile women. Their success of implantation and progression to pregnancy is also very high so the yield is typically very good. Because of the combination of their age, plus the requirement to transfer fewer of the embryos that are derived from those women, they do have extra embryos that obviously predominantly are used for that couple's future family building, but certainly would have materials that could be used for research. One of the complicating features is that there is compensation for these individuals that is proscribed by prop 71. Thinking conceptually about how one might be able to separate compensation for a certain number of oocytes for purposes of IVF and noncompensation for one that would go to toward research purposes needs to be further discussed. These women are also likely motivated somewhat differently that those who would present for oocyte donation for pure scientific purposes.

Eggan: There is even a broader issues at stake in this situation, because f the infertility of the couple that's being donated for and the fact that at least through the structure of the payment for IVF, essentially the infertile couple bears the cost of the woman's oocyte donation. Those oocytes, in a de facto sense become that women's eggs and they are relying on those eggs to treat their infertility. In my mind, with compelling evidence I could be convinced otherwise, it seems that this is in a sense de facto the same as diverting the [donor's] own eggs from her own reproductive efforts. The primary thing to be concerned with here is the potential conflict of interest between the clinician and the patient and the clinician and the research scientist with whom he's collaborating. There needs to be some sort of systematic discussion

addressing how that conflict of interest can be resolved because this is a central concern.

Cibelli: What is the likelihood of a couple coming in to an IVF clinic and offering to donate half of the oocytes retrieved in the IVF cycle for research?

Taylor: I'm not aware of this situation coming up before, but it is not completely unusual to have a single donor have two sets of couples approach that donor to have her split her available oocytes for cost-sharing purposes—there have been shared donors. There has been some discussion of this within the IVF practices as to whether you create conflicts and issues when one couple get s pregnant and the other does not. I don't see it being intrinsically different than a split between a scientific project and a fertility seeking couple, but admittedly there are concerns. For example, if a fertility-seeking couple fails to get pregnant using the eggs available may wonder if the pregnancy outcome may be different if they had the eggs donated for research available to them as well.

Eggan: If that is preprescribed before the procedure actually takes place, it could be that neither couple got pregnant from the donation too. One thing I would be concerned about is there some sort of objective criterion that can be used for splitting those donated eggs into two pools—if you are splitting the material, is it unbiased? Is there a chance for the couple trying to get pregnant to worry about [the potential for this type of bias]?

Taylor: Typically you would want to identify the healthiest, typically largest follicles for fertility purposes; and if there were smaller follicles that could be oocytes that could be recovered, you might call them "second rate". The truth is, the correlation between follicle size and oocyte quality isn't linear. There is some question now about some of the criteria that we use for identifying what is a good looking follicle. It is a bit of a gray area. You can see how many follicles on ultrasound there are, but typically, you get 80 % of that number in terms of oocytes recovered, but there are exceptions to that rule. In some cases you may think you are going to get 30 eggs and you only get seven—that would change your manage in midstream.

Cibelli: Did you ever get a donor that donated for free

Taylor: We've not had that experience in san Francisco.

Cibelli: Compensation is prohibited under prop 71

Taylor: Ann has had experience getting donors that are just compensated for their time.

[point of clarification posed to James Harrison]

Lo: my understanding is that prop 71 does not allow us to compensate for time, only for out-of-pocket expenses for donation.

Kiessling: but the term "out-of-pocket expenses that was hotly debated in Massachusetts—we got involved in that debate. They do not use the term out-of-pocket

Harrison: The specific language reads "standards prohibiting compensation to research donors or participants while permitting reimbursement of expenses."

Kiessling: So it become a definition of expenses.

Lo: Does that include compensation for time

Harrison: bob Klein has indicated that his intent in writing this provision into prop 71 excludes compensation for time, including lost income.

Eggan: In this same vein, it may be a perhaps more important thing to discuss the source of material which is currently being used in Great Britain fro nuclear transplantation experiments, which are failure to fertilize oocyte. It is important to for this panel to make some sort of statement or to at least have a discourse on the topic of the use of these oocytes and what we think the concerns or benefits there are.

Lo: We should separate this and make this a separate topic of discussion.

Kiessling: One of the ways this might work is to have a clinic, as there is England, in which the entire policy of that clinic is that some of the eggs go to research. If that were a clinic wide policy so that everyone who approached that clinic [was aware of this policy]—decisions would not in this case be made via a patient-by-patient consent process. I don't know how you are going to work around the expenses issue—you may be able to use some of the eggs for research under those circumstances. Other than that, I can't think of a patient-by-patient scenario in which you are going to have people being able to donate eggs, either shared eggs from their donors or donate eggs themselves for research.

Eggan: That whole clinic would have to function under the policy that none of the donors could be compensated.

Cibelli: [question posed to Taylor]. Do you ever have couples that come in which the woman is fertile and offers to donate half of here eggs to another infertile woman or to be frozen for later use—they don't want to fertilize more eggs that they actually need?

Taylor: Our ability to freeze eggs successfully is still not very good. It is improving and there are some programs that have had some success doing that, but there are not that many programs around the country. Those that do have egg freezing protocols are experimental protocols at this time. In general, what couples will do is they will fertilize the number of oocytes that they generate even with the expectation that may only transfer some of them. The remaining embryos that are made can either be destroyed , frozen for future use, or donated to other couples—in an embryos adoption. There are extra embryos. They've already missed the opportunity to be fertilized maybe with the sperm of another partner for another couple—so it's a little different from egg donation.

Cibelli: So we don't have to worry abut that—we are not going to get "spare eggs" from a couple.

Taylor: Certainly it is going to be feasible to get spare eggs. [sentence interruption]

Cibelli: If California decides to go forward with this research and things are going well and we see a lot of progress, maybe some people will start coming forward and say "if I can give you more than ten [oocytes] then 5 of these may go to research.

Eggan: that is also troubling because what does it mean to be a "spare" oocyte? If the couple is infertile, they need every egg they've got in order to get pregnant. As a scientist, I would like to think this is a very worthwhile and reasonable source of material. When an infertile couple come to a doctor and they're undergoing medical treatment to treat their infertility, it seems like it is the doctor's responsibility to do everything in his/her power to give that couple a baby. That is why they are there, first and foremost. Even if the woman is infertile and the man is infertile for unknown reasons—you may need to fertilize every single one of those eggs or attempt to do so in order to give that couple the best chance of having a child. It may be a difficult thing to compute how many of those eggs are "safe" to be donated to

research and still protect the couple's opportunity to have a baby.

Cibelli: I'm am concerned with the consent scenario which is what we're discussing today. I'm not talking about the ethics of coercing couples to start donating eggs because they have bigger problems on their mind. But if they want to do it for any reason-do we have appropriate consent forms [for this purpose]? Are we going to have a cooling off period in this case?

Taylor: I don't know if this is where you want the discussion to go< but Jose raises an interesting scenario where in a known case of male factor where there's a low sperm count and you are planning to ICSI, [a procedure in which sperm is injected directly into an egg] and if you were to collect a lot of eggs from an otherwise probably fertile woman who just hasn't been successful because her [partner is infertile- you could get ten eggs five of which could be left over that could potentially be used for research purposes [given that it would be technically difficult to do ICSI on that many cases in a given period of time] if that couple were appropriately consented up front.

Lo: Jose raised a point that we need to keep in mind. Although we talk about the context of consent. This is a much bigger issues. I don't think we can separate consent from the whole issue of the ethics of donating oocytes simultaneously for research and clinical care. At the risk of confusing, we need to combine those two issues just for this topic.

Hall; It seems to me that the problem is if you don't want to take the eggs for research purposes until you know that you've exhausted all possible remedies for fertility purposes. By the time you know that you have a successful pregnancy, the eggs are no longer useful. I see this as a real complication in terms of that scenario. There may be specific situations such as the one mentioned which is probably relatively rare where there might be cases in which [women would donate "excess" oocytes] but as a general rule, it poses a real ethical dilemma.

Lo: Is it so tricky that we should not allow CIRM funds to be used for these kinds of oocytes?

Feit: unless we are sure that there is success with the couple and the pregnancy, I don't think we can because [the donor] will always wonder if the donated eggs may have resulted in a pregnancy.

Prieto: before we completely preclude it, we should consider that what we are looking at is the current state of the art which could change and almost certainly will change in terms of the difficulty in obtaining oocytes [in terms of the rate/probability of success you can offer a couple [seeking infertility treatment] if we anticipate this changing in the coming years at least put appropriate safeguards in place, even though we don't have anyone coming forward now, five years form now we conceivably could.

Lo: Another option would be to say at this time we don't permit it but leave it open to change.

Eggan: I would encourage that. If we do see that oocyte freezing becomes a viable option, that's going to change the entire landscape immediately. There are certain clinics that specialize in male infertility and most certainly there are surplus eggs at such a clinic. Example: Sherman Silber's research in sty. Louis, mo. I would hesitate to preclude it. I don't know how to balance these two concerns beside walking through the various possibilities very explicitly.

Hall: It's simple. You have a phrase that includes "until fertility is ensured." The priority has to be fertility first and research second. Only after one has tested all possibilities for fertility can then research be considered. [

Eggan: Suggests opening for public comments.

Lo: Agreed, [addressing Kiessling] you thought through this and chose not to try and recruit oocyte donors for research through IVF practices.

Kiessling: Correct.

Lo: Can you provide the background [for this decision?]

Kiessling: The practice of IVF and attempting fertility for couples is really different from what you would do for somebody coming through [this process] for research purposes. Part of the difference is the risk of OHSS. People who are going through an infertility cycle are willing to risk that to just get three or four more eggs. That is not something you can do for people who are simply involved in a research protocol. So you end up on the very far side of being very, very conservative in terms of how much stimulation the donors for research purposes are given. The egg collection numbers are much, much lower, but simultaneously the risk of any kind of ovarian complication are also either zero or much, much lower. Plus the fact that donor screening for research purposes is different from donor screening for infertility in that the practice of recruiting donors for infertility has defaulted more to specialists in that area. They also screen people for genetic diseases [even histories of alcoholism which is not something that you necessarily need to screen people for if they're donating eggs for stem cell derivation.] So though the history-taking is different, the acceptance criteria are also different. So we started using all the criteria from an infertility practice, and systematically adapted those guidelines when we realized that what we were doing was so different from family planning.

Taylor: I think that's exactly right, I might argue that screening by history for donors that may be used to derive therapeutic stem cell lines might, in fact, need to be more rigorous than it is for infertile couples if we're talking about therapeutic uses. I'm a proponent for the ability to recontact individuals to identify diseases that may develop later on in their lives. It's also going to be extremely important up front, if we're talking about using these cells as therapeutic agents, to make sure that we're being as rigorous about the quality of their genetic background, etc., etc., as we possibly can be.

Kiessling: I think that the donors for research are actually more open to being recontacted than the donors who donate eggs for fertility. I think people who have donated eggs for fertility want to remain anonymous by and large, and I think the women who are willing to do this for research purposes, they want their confidentiality protected, but I think they [would be willing] to be recontacted should the science need it.

Lo: So what I'm hearing is ethical concerns about allowing women to simultaneously donate oocytes for research and for IVF, that at the current time freezing not being an option, if we allow it to happen at all, it would have to be under pretty exceptional circumstances, like male infertility or a clinic that requires it. So let us try and craft language that at least discourages this and perhaps prohibits it except for certain exceptions. [Invitation to any members of the public who want to comment on issue of simultaneously donating oocytes for both research and IVF].

Reed: Down the line, the CIRM should consider finding a way to compensate oocyte donors.

Reynolds: There have been serious the issues in the press around properly sourcing eggs for research. Glad to see the sense of the board is that the fertility comes first and then the research second. I think you'd agree that the health of the woman comes before either of those.
And a couple of very important points--Eggan brought up the concern that the doctor responsible for the egg extraction might find him or herself in a situation of a conflict between serving the interests of the patient and the interests of the researchers. Kiessling brought up how this gets more complicated when

you can get many more eggs by administering more hormones, which raises the risk of medical complications. [Center for Genetics and Society] has advocated having a physician who is fully independent of the research be responsible for the entire egg extraction process, both medically and probably also for the informed consent, a physician who is not affiliated with the research or receiving any type of compensation for the eggs. That would help build in a firewall between the interests of the research and those of the patient.

Lo: This is similar to, for example, the requirements we have in transplantation, that the person who retrieves the organ not be responsible for the clinical care of the patient who's the donor, in the cadaveric case, of the live donor in a living donor case.

Taylor: Your final recommendation went beyond that, and that would be suggesting that a third-party surgeon do the nephrectomy for the renal transplantation. As a clinician who's spent a lot of time in clinical training, I would want to know that that procedure was being done under the best possible circumstances. It's an interesting model. It would mean that there would be a stem cell retrieval center, clinic where everybody was clinically trained and had all the experience that an experienced IVF physician would have, yet was not being remunerated for that. And it's kind of a curious model, but under the right circumstances, I would be able to accept that.

Eggan: To expand on this issue of compensation for egg donation-- it's important to make the statement there are many people that believe that this course that we're taking, which is prescribed by California law, is the wrong one. I think we should acknowledge that. There are laws in the United States which also state which people should have equal access to the ability to participate in human subjects' research. And there are those that believe that by not compensating, you restrict certain people from being able to participate. Indeed, as you say, there are many people who have relatives suffering from debilitating disease who believe, true or not, that this research might help their loved ones and are interested in participating. It's fair to say that many of those people will not be able to participate because we will not be able to compensate. Nonetheless, the law is specific to this issue, and I think that's where we have to look to that.

Kiessling: The statute is interesting in that it allows compensation for everyone involved except the donor. The doctors are to be compensated, the clinics will be compensated, certainly the drugs will be purchased. So the only individual who's part of this very expensive process and it costs about 20 or $25,000 for an oocyte collection who will not be compensated for their time is the donor. And I think it's simply a matter of how you interpret expenses. I don't think that this is an insurmountable problem with the California statute.

Rowley: Isn't that true for all organ donation? The only person not compensated for the kidney is the donor?

Eggan: This is true, but then it's a question of whether or not oocytes are like kidney or whether or not they're like sperm or blood. It's true that the risks of donating oocytes are greater than risks of donating blood, but they may not be as severe as the risks of donating a kidney. And so this has been one of the problems with oocyte donation and compensation is that it's hard for us to decide which one of those things it's like.

Lo: The law is written and cannot at this point be amended. Since the author of the proposition is on record as saying he interprets it to mean we can't pay people for their time, I think at this point it's a matter of having to change the law.

Cibelli: There are cases where, for example, some women, young women may have been diagnosed

with cancer and have to undergo chemotherapy or radiotherapy which would wipe-out of all the germ cells and now there are protocols where they can freeze their pieces of ovary and be later used for making babies if they need to. I wonder what we're going to say about donating materials that can be later used as a source of eggs. Even in the cases of ovarian cancer, you may still have pieces of the ovary that can be -- you can mature eggs in vitro even though that technology is not quite ready.

Lo: I think that we need to be open to [that possibility] in the future, if that becomes widespread and available and sort of an accepted practice, to allow that to be another pathway.

Eggan: I would go further than that. I would suggest that this a particular type of research that CIRM should decide to fund, that it should encourage research in oocyte freezing, that it might Consider RFA's for alternative sources of oocytes. It might encourage research on in vitro maturation of eggs, over optimized material from cancer patients because these are the sorts of enabling advances that we need in stem cell science to take oocyte donation off the table. And they're within reach. They're just not being done because there's not a [primary] interest.

Cooney [member of the public from the GTU]: Is it possible that if the procedures for freezing oocytes improved in the future, that a young woman who is donating eggs could be compensated by having some of her eggs frozen in case she could not, in fact, become pregnant in the future?

Lo: Moving to other topics.

- Donation of embryos as opposed to oocytes
- Criteria for use of human embryonic stem cell lines which are not derived with CIRM funding, but which CIRM-funded researchers wish to use
- Failure-to-fertilize oocytes;
    - Do we want to characterize the key features of consent that need to be present in those lines?
    - Do you want to talk about failed to fertilize oocytes as a potential source of materials for derivation of new stem cells? As background, when Rob [Taylor] was at UCSF we thought about this a lot, actually had approved a protocol for that. And we thought the key issue was how is that determination of failed to fertilize made? And we said that if the embryologist making that determination was totally independent of the research team and did not know when he or she was making the decision to discard or not whether it could be used for research, that that would ensure an absolutely objective assessment. And only after you decided it was going to be thrown out, could you see whether or not the donor agreed to allow it to be used for research, but to make sure there was no kind of shading of the determination of failed to fertilize because the person making that determination knew it might be used for research.

Taylor: That kind of blinding was actually quite easy for us in our own IVF program [at UCSF] just because the embryology laboratory is isolated and is fairly high throughput place. All the materials get handled the same way, and it's not clear to the embryologist whether patients had consented to the research protocol or not. Typically, we would do an insemination of the fresh oocytes, and if they failed to fertilize, there was a period of time where we were doing what we call a second day insemination or we'd ask the partner to come back in with a fresh sperm sample and try to inseminate the second day. Typically it was extremely rare, quite honestly, for those second day inseminations to ever be successful. So I think in thinking about unfertilized oocytes as a possible source, I think that most IVF practices would feel that if there's a failure to fertilize in the first day, that those oocytes are very unlikely to fertilize naturally or with ICSI and that those potentially could be set side for this type of research. One of the concerns that we had in San Francisco using this failed to fertilize oocyte model was that we knew we'd be kind of working with materials that probably were less likely to succeed, and that becomes even more

problematic if you extend the length of time in culture. That was the thinking and practice a the time. If one were to decide at the end of the first day that failed to fertilize oocytes might be eligible then for experimentation, and that would have to de facto mean that nobody wanted to do anything more with them in the clinical laboratory, it would be a source of material, but I would suspect, given the relatively low rates of success with nuclear transfer, etc., now, I think it would be even worse probably in this setting, but it's something to be considered. It gets around a lot of the ethical issues.

Eggan: That is the one primary ethical issue with failed to fertilize oocytes is the difficult position it puts the IVF clinician in if there's a conflict of interest. So if there is some reasonably prescribed mechanism which can take that out of equation, as you just said, you only know after the disposal whether or not they're going to go for research, then in my opinion that's discarded medical waste, and it's something that obviously can be used for research. It would be interesting to know more about what that mechanism would be like specifically. It could a situation where do the scientific benefits outweigh the ethical challenges to the material? If you can take care of that one central issue, and if you're really certain about the timing in your clinic when you're going to make that decision about failed to fertilize in the absolute sense, then to me that seems reasonable.

Kiessling: I don't think this poses a problem for the clinical lab. I think IVF labs have pretty cut and dried routines about when they decide something is going to go forward. The single problem with failed to fertilize eggs is where did the sperm go? And if the egg was fertilized naturally, if it was fertilized, inseminated in a dish, that egg is absolutely covered with sperm probably. They didn't get in and something didn't happen, but they're still there. If that failed to fertilize egg had undergone this intracytoplasmic sperm injection and it didn't fertilize, where is the sperm? So if you activate that egg, what's happened? have you, in fact -- you activated it and it really is fertilized and it just didn't look fertilized in the IVF setting, or does that matter? In California it obviously doesn't matter because you can fertilize eggs in California to derive stem cells. In Massachusetts you cannot. So we specifically are blocked from using any kind of fertilization procedures. So Massachusetts, somehow you would have to ascertain where the sperm are and what happened to the sperm that failed to fertilize egg so you would not run the risk of actually activating a quiescent sperm and, in fact, fertilizing it by mistake. I think the single biggest issue from the biology standpoint is what happened to the sperm.

Taylor: There's some very interesting scientific questions that come up. It might be that introducing another nucleus, you could reactivate and end up with triploid cells, and it could get really kind of curious and complicated as you think about it. One of the underlying principles is that a failed to fertilize egg may well have some intrinsic abnormalities within it that might not make it the world's greatest candidate therapeutic stem cell research. I don't think we should discount the importance of karyotypically, chromosomally abnormal eggs and embryos that could be really wonderful research tools to understand better down syndrome and turner's syndrome and other diseases that we would want to study and understand better in the laboratory. Those are things that should come from CIRM, so we may really want to have -- be able to propagate cells from abnormal eggs and abnormal sperm and abnormal embryos, but for the therapeutic purpose of generating stem cells for treating patients, I think that we might not want to start with kind of a low common denominator that you might get with an unfertilized egg.

Lo: What I'm hearing is that if the various concerns that have been raised, particularly the conflict of interest concern, could be worked out, this could be another acceptable approach, but we want to specify pretty carefully how we make that determination of failed to fertilize in an objective and unbiased manner.

Taylor: [Addressing] some of the potential consequences might be in terms of outcome.

Lo: What about Embryonic stem cell lines that CIRM doesn't fund, what should be the restrictions we place on how those lines are derived and the consent for them?

Eggan: Do we want to talk about donated embryos? We may imagine having more specific requirements for what can be derived under CIRM funding than what we allow in, and so I'm wondering if we cast the larger net. That's just a suggestion.

Lo: Let's talk about primarily donation of frozen embryos that were originally intended for IVF, and now the couple in IVF has made the decision rather than discard or give to another couple for their fertility treatment, to donate them for research.

Eggan: The NAS guidelines speak very clearly to this issue, and they say that these embryos should be frozen to dissociate the decision to donate from the reproductive effort. This seems, in the case of these embryos, a very reasonable thing to do. However, I think there are certain exceptions to this rule that should be allowed. In fact, that I think are explicit in the way the Guidelines are stated. And there are certain types of embryos, such as PGD embryos, which should be allowed to be donated in an unfrozen state. I think really what's happening is, again, there are certain types of embryos which will always be discarded and will never be used for reproduction of that woman. In the case of the couple undergoing preimplantation genetic diagnosis, those are the embryos which are affected by the disease as determined by genotype. Those are always going to be thrown away and never transferred into the woman's uterus. Therefore, it seems to me there should be no requirement to freeze some embryos before they're donated for research. In fact, these, for scientists, a very important source of material because they would allow researchers to derive embryonic stem cell lines which carry disease genes. So I think that should certainly be one exception to this rule. In no circumstances would there be a diversion of material away from the woman's reproductive efforts. Likewise, there may be other types of embryos that by absolutely objective criterion would be okay. For instance, in some practices that multinucleate cellular embryos are never transferred-- affected embryos after PGD are never transferred, but it may be that in some circumstances these other types of embryos that one might consider as never transferred at other clinics <u>are</u> transferred. There are certain types of embryos which we could absolutely never need to be frozen, others there's room for expansion, I think you can move into a gray area. That's certainly one thing that I, as a scientist, would like to make sure is clearly stated.

Cibelli: How the consent form should be crafted for the embryos?

Lo: As with the fresh oocytes, should we allow it at all? If we don't allow certain things, then we don't have to worry about it.

Eggan: This is important with respect to consent because allowing donation of these types of embryos requires a totally different consent structure.

Cibelli: Agreed. I just want to know how we move from here. I agree with Kevin, that we should use the frozen and the fresh [oocytes] that have some mutations. They're going to be thrown away anyway.

Taylor: The timing of the consenting process, though, might be different, on these two. You can see certainly having a long time-out period when your excess embryos have been frozen. You've got quite a short time-out period if there are fresh embryos in the laboratory that have selected neither to freeze them nor to transfer them back into the uterus. those embryos have a short period of time in which some disposition decision would need to be made.

Kiessling: True. Something like 10 percent of eggs are triploid within the first 24 hours, 8 to 10 percent, and that seems to be universal. Every IVF clinic would have to have that caveat in their consent form. It

would have to be ahead of time. This might happen, and we'd like to give that for research--Kevin is talking about the triploid.

Eggan: Primarily I'm talking about PGD.

Kiessling: The PGD embryos is a very, very long time-out. I can see working out a consent form for that really easily.

Eggan: For PGD the time-out would be at the time the couple presents to undergo PGD and says that we're going to sign a clinical consent to undergo PGD, there might also be a check box in that consent for which would say if we have affected embryos, not carriers, not normal embryos that might be used for our own reproduction, but if we have affected embryos that would be discarded, then we will give them up [for research purposes]. They would have to presumably reconsent at the exact time when those embryos are donated. So essentially the entire course of their care as a time-out. One could do the same sort of thing with triploid embryos, but that seems a little bit riskier because I understand sometimes not all the cells might be triploid, and sometimes they're transferred just as a last resort.

Taylor: They tend to be sort of late observations. Switzerland, which isn't maybe a very relevant example for us, but there I think you can only transfer two embryos. So what their practice there is to maybe have four embryos growing in the dish, you select the two very best embryos that transfer back to the recipient, and they're forced to destroy the other two embryos. If we were in a setting like that, that would be another situation, but I don't know if we're going to be getting CIRM-approved embryos from Switzerland, but I can't think of too many other scenarios.

Cibelli/ Taylor: they use the fresh.

Feit: Aren't we getting back to your idea of right from the beginning of providing a clear consent process so that donors understand what they are entering into in the cases in which you know the fate of the cells?

Kiessling: I can see the entire infertility community being willing to put out some kind of blanket policy that affected embryos are available for research. I don't think anybody would object to that. I think that could be something that's routine.

Taylor: Although degranulating or degenerating cells within an embryo, we've certainly seen good pregnancy outcomes.

Kiessling: No. I mean the ones that are going to go through PGD.

Taylor: Yes. But if you get a little bit softer than a real genetic diagnosis, determining just on visual criteria alone, it may be hard for everyone way of assessing good versus bad embryo.

Eggan: As another, important criterion, if a couple undergoes PGD and they have three embryos from the procedure, and all three of those embryos are affected by the disease, they transfer zero embryos. I think that should be the cutoff. Because if a couple undergoes IVF and they have three embryos and all three embryos are potentially triploid or have abnormal morphology, it probably is true that all three of those embryos are transferred routinely. I think that's a very important distinction that we need to take into account because, again, that speaks to diversion of the material from one purpose to another.

Prieto: Even with PGD, this needs to be a part of the consent process up front, that those women are aware of this possibility. I can't imagine there being many disagreements.

Lo: I think that's understood, but needs to be explicit. Do we need to say anything about embryo donation when the embryos are frozen and the couple completes their reproductive goals in terms of the kinds of protections?

Eggan: There are some interesting issues to consider with respect to recontacting people after PGD too. I can tell you, as a scientist, when you have a couple that undergoes PGD and you wish to obtain the affected embryos which would manifest the phenotype of the disease, presumably in tissue culture after derivation of stem cell lines, as a control, it would be very useful and interesting to have ES cells derived from the carrier embryos as well as the unaffected embryos from that same couple. It may be that if they're very successful in their attempts, that they'll have other left-over embryos with the same sorts of genotypes in the freezer once they've completed their family. It would be very useful to be able to recontact those families and have them donate those embryos just as other couples who have finished their family donate embryos. So I think that's something that we should encourage or figure out how to work into this PGD consent, which is a different type of thing. So this might be one rare example where it may be worthwhile to recontact the family. There may not be the same stigma to recontacting these people because they're presumably undergoing IVF, not because they're infertile, but because they have these other concerns of overt disease in their family. So the need to contact them to study their disease that runs in their family may far outweigh the negative connotation of recontact.

Cibelli: Is there any need to indicate a certain period of time that has to pass to make sure the couple is really done with family planning to say, okay, now you can't donate. Let's say they're in their twenties. They're done, they think they're done, and they want to donate everything, and then later on something happens, you can't have any more children?

Taylor: That's a challenge. We're getting embarrassingly good at getting 50-year-old women pregnant with donated embryos. So it can be a little bit hard to know when to draw the line. I think there are some sort of other evolving issues in society, and one is later pregnancies as a result of postponing pregnancy and developing careers. Couples that have donated and frozen embryos will always have the right to maintain those embryos in a frozen state and be able to use them and release them at a time that they make that decision. I don't think that's something that we're going to usurp from them, but trying to decide when is an appropriate time to contact them or how long is too long, I don't know that we're going to be able to resolve that question very easily. The other is that there's kind of a recent development of embryo adoption programs that have come up as a really response to the large number of frozen and unused embryos that currently exist around the country now in IVF program freezers. Many infertile couples now are beginning to go to some of these programs to actually adopt these healthy -- they're typically healthy embryos because the reasons that nobody took them out of the freezer is because they got pregnant with their first two embryo transfers and have the family that they want, and these are really indeed excess embryos. So those should healthy, viable embryos. Now they're being donated to other couples for fertility purposes.

Cibelli: And it's true there are many that are frozen, but are we just being too aggressive on that on end? How about the couple that have different plans? They didn't think it through very well. Do we have to give them six months to think about it? What would be the approach? How would you do this?

Kiessling: Frequently the pressure is put on these couples by the clinic. The clinics have a timeline that they want to store these embryos. And the couple has to make a decision, or they have to start paying in some circumstances substantial amounts of money to maintain their embryos there. So the pressure is not being put by the research community. the pressure is put on these couples by the clinics. And those guidelines are probably mostly driven by a need to keep contact with these people because if they wander off and you've lost contact with them and you don't have a default mechanism for doing

something with their embryos, you're stuck with a huge population. And there's a lot of clinics with that problem now. The couples have just wandered off, and we can't find them anymore, so they're left with these embryos. That's not a trivial problem. So clinics have gotten a lot more aggressive about forcing people to make decisions about what they have in the cryo bank.

Lo: My understanding is that typically what happens is if you have embryos frozen in an IVF clinic, every year they send you -- they contact you and you've agreed to this up front, and you're asked would you like to pay your next month's freezer storage to keep them in the freezer? Option b is would you like to donate to another couple for reproductive purposes. Third option is would you like to just destroy them? And fourth option would you like to, instead of destroying them, donate them to a researcher for research purposes? So it really comes as sort of an annual time to renew your sort of little parking permit at the storage freezer.

Taylor: Unfortunately a lot of people choose the fifth option. When you're running an IVF program, there are a lot of people who actually don't get back to you. And we're very reluctant to do anything other than just keep the embryos in storage, but it does become an economics issue at some level too.

lo: Contact is never, as I understand it, initiated by a researcher. The woman or couple needs to make some indication that they're willing to consider research, and then they're put in contact with the researcher.

Cibelli: What you're saying is that we're going to have to worry that there are so many embryos stored, and we're not going to drain the banks, and we're not going to be competing with couples that may change their mind in the future.

Lo: You raise the important point, Jose, that there's always someone who can donate and a couple years later some tragedy occurs and their kids are in a car accident, and say, well, my gosh, now I wish we had those frozen embryos and hadn't given them for research. There's always that kind of unforeseen calamity. Otherwise, I think most couples, if they can afford it, just keep storing these frozen embryos for long periods of time if they're not really sure they want to give them up for research purposes.

Hall: I understand there's a man in Florida who has made an estimate of the number of embryos in storage and how many of those have already been consented for research purposes. And the claim is that something on the order of 10,000 embryos could be used for research if there were funds available to study them. I advance that very tentatively, but that's my understanding that there's quite a large number of these embryos that already have been consented for research, but there is no outlet for their use right now, no research outlet.

Taylor: It sounds very reasonable. I don't know the statistics any better than that, but there are a lot of embryos that have been completed families, embryos have been assigned over for research protocols, and kind of are waiting to be used.

Hall: The estimate is about 5 percent of those -- 4 to 5 percent of those that had been stored had been consented for research purposes.

Rowley: it's my impression that or scientists who are really seriously into the developing stem cell lines, and I think I heard this from the practice of Doug Melton's laboratory. He works with one IVF clinic that he knows has very good practices of both fertilization and culturing, maintaining the embryos such that embryos obtained from that particular practice have a higher likelihood of success than just going off to clinic a that you've never had experience with and getting these embryos. I realize that's a practical

problem, not an ethical issue, but I think one has to sort out what are really acceptable frozen embryos as compared with 600,000 in people's freezers that individuals wouldn't really go to because you are going to get one or two from this clinic and two or three from that clinic.

Eggan: The real difficulty is that these experiments have so many moving parts and they're regulated at such a high level, that you want to have a high level of confidence and trust with the IVF collaborator, and you want to understand very carefully what they're doing at every level. I think that the inconsistencies and the reports coming out of Korea and what is apparently a lack of communication between the two hands of the same experiment there lead us to note how important it is to have a close relationship, a specific relationship, a collaborative open relationship with the group which is doing this clinical practice. I think it's critical. I think not just for scientific reasons, but to assure the ethical standards of the experiments which are being done.

Taylor: I think those are all extremely important points, and in particular the ethical aspects of it. It's published actually. IVF programs around the US are mandated to report their statistics to the CDC, and those statistics are actually audited. So one can go through and find out what the success rate is of one program versus another. They're quite variable across the country. But I say that the practice of embryo freezing is a fairly selective practice. Because of the costs involved with embryo freezing, you don't just freeze every embryo that you've created. So by the time the decision is made in the embryology laboratory, that an embryo that hasn't been transferred back into the patient is going to be frozen, those embryos, at least morphologically, have the appearance that they're going to be viable, healthy embryos. so I would argue that the embryos that are frozen are the embryos with the greatest likelihood of success of developing into babies or into stem cell lines as far as we understand it. So I think that we do have some reasonably good material to work with if we can get to it.

Kiessling: There are a couple of recent reports that you can derive stem cell lines from biopsied embryos, fresh embryos with one cell. Is that anything that we need to discuss?

Eggan: This is something that we probably should speak to. This is the paper about Bob Lansa's report (in ACT) about derivation, at least work carried out in mouse which reported essentially that you could a single blastomere from a preimplantation mouse embryo at the eight-cell stage, co-culture that with an existing embryonic stem cell line, and derive a new embryonic stem cell line from that blastomere. Essentially this was based on the premise that you couldn't destroy the embryo in the course of deriving the stem cell line in that way. There's two primary things to say about that, in my opinion. One is that's not an issue for us to really consider as a group because the California legislation has already said that destroying an embryo is okay. Essentially there's no need, in my opinion, to do that type of experiment because essentially California legislation says it's okay to destroy the blastocyst to derive embryonic stem cell lines. That was the purpose of the experiment. And then I would further go to say that if you are someone who feels that these embryos must be protected and you take that position, then I think the experiment is troubling in that sense because I think you would never expose a person to such a potentially dangerous procedure for no particular gain of their own. Although I think this is scientifically a very interesting experiment and it's interesting that it demonstrates that one can derive these types of cell lines, and I think that these types of experiments are interesting from a human embryological and people in California might want to do them and we should encourage them to do them from that perspective. We certainly shouldn't encourage them to do that type of experiment because it protects the stage of human embryo.

Cibelli: I kind of disagree with that. I think there are so many other better experiments to do and better ways to spend the money. But if you get an idea and you send a proposal to see -- you are going to some proposals from people maybe perhaps from ACT sending in a proposal and tell you I want to do it in human. Would CIRM pay for it or not? They've done it in the mouse. Sooner or later in human.

The efficiency was very low. It was about 10 percent. So for every ten blastomeres, one produced a cell line. But if you are going to have a child and if you are willing to do PGD, you are really risking the embryo to take one blastomere out, I would argue that just having your custom made embryonic stem cells maybe cheaper than somatic cell nuclear transfer. You don't have to wait for the donation you eggs. Why not?

Eggan: This is a very specific and different case though, right. So PGD is okay presumably because you're ensuring the health of a future child and the treatment. So, again, I do not hold this perspective, so I am merely arguing from the perspective of one that would say that we should not as a society destroy these embryos. That's a point of view I do not hold. I think one first has to be at that particular point of view to say that. So then I agree, this is a different situation. Now if as a course of treatment if one was undergoing IVF and one wanted to make a genetically tailored stem cell line for their own child, and one thought that this -- I think one would have to ask is the benefit that one would have by deriving that patient-specific stem cell line outweigh the risk to that future child too. If that's the clinical equation, then I think that's the one we have to meet. I think that's a good idea. If one weighs that equation and find the answer is yes, then I think absolutely.
again, to say very clearly, from the scientific point of view, I think these types of experiments are very interesting. Since we hold that these things are human embryos, but are not people, it is perfectly understandable that we would subject them to these types of experiments. It's perfectly reasonable.

Cibelli: CIRM as an entity will get proposals. What happens if you get a very good proposal that wants to do this, that wants to derive human ES cells for eight-cell embryos?

Eggan: I think that's something we should fund because it's a type of embryology that we should understand.

Hall: The question that we're concerned with here is what are the issues for the donor and the consent for that; isn't that correct? Our issue is not should we fund that research here. I think, unless you want to consider that it should be prohibited, but I think the issue here is that a donor class we want to address as we work our way through these issues. Isn't that right?

Eggan: That's right.

Kiessling: I just asked if we needed to talk about this as a new report.

Taylor: I don't see it as an outlier particularly. As far as I know, blastomere biopsy from human embryos, I don't know how successfully it's been from thawed embryos-typically it's done in a fresh embryo setting, so it may be one of these situations. And we don't have too many fresh human embryos that are going to be donated to science, but this might be one of the interesting ways to go. I completely agree with Jose that these are extremely important experiments to do because ultimately you want to have -- every embryo, every fetus, every baby would have its own embryonic stem cell line potentially. It would a lot better than cord blood research that we're doing in some settings. If that's really the end point that you want to get to, the time to do it would be if you could demonstrate that it's safe to biopsy a single cell blastomere from an embryo at the eight-cell stage and go on, which I expect we're going to be technologically able to do that pretty well. So I think that it would be an appropriate thing to fund.

Cibelli: This would be a case where we had to obtain a consent form for a healthy, otherwise healthy fresh human embryo.

Taylor: I think you wouldn't know the health necessarily.

Eggan: Correct me if I'm wrong, but embryos are often frozen at the four or the eight-cell stage; isn't that correct? So since this is an experimental technique, this would have not to be any different from the normal -- in principle the normal consent that we do for stem cell derivation. It's just that the consent would be specific to this experiment. it would be a situation where, of course, people who have some blastocysts can't contribute or can't participate, but those who have frozen four-cell or eight-cell embryos, they could donate their embryos, which would then be thawed and each of the blastomeres or one individual blastomere would be biopsied out and
used for this experimental approach to see if the same thing that was true in mouse was possible in human. This seems like a very reasonable thing.

Taylor: I've seen frozen thawed grown embryos biopsied.

Eggan: that might be a worthwhile research goal.

lo: Let me suggest that we sort of separate out where the stands on the list of research priorities from other distinct consent issues. After we write up what we've discussed today, there's a lot of ground we covered on all the other categories, to then ask Ann, Jose, and Kevin to come
back to this as a special case and see if there are special consent issues in this situation that would need some additional guidelines, but not to try do it till we've actually seen how we're going to handle our sort of more common paradigmatic cases. I actually think we've done a lot so far, and I want to keep us fresh, so I was going to suggest that we actually take a break now if that's okay with people unless you want to keep working.

(a recess was taken.)

[Report on the CIRM Grants Administration Policy by Dr, Arlene Chiu]

Chiu: CIRM staff has been working on a guidance statement for grantees, and that means individuals and institutions that will be receiving CIRM awards. And the goal is to have a comprehensive CIRM grants administration policy for this purpose. So today what I'd like to provide this working group with is an update on our progress in crafting such a document and what I plan to do is to review briefly the background and the purpose for such a policy statement, present for you a brief synopsis on its contents, and then end with a current status of different drafts of this document. first a brief background.

Background

- In may of this year, the CIRM issued a request for applications to support training grants that will train at research and academic institutions in California the next generation of stem cell scientists and clinicians.
- twenty-six applications were received and subsequently reviewed by our scientific and medical research funding working group.
- Their evaluations and recommendations were then presented to the ICOC at their September meeting, and the board approved 16 of these training grants for -- these training applications for funding.
- in order to for CIRM to implement these awards once bridge funding becomes available, we have to set up the necessary infrastructure to do so.
- That means that before funding can take place, we have to complete three tasks.
    - The first, if you can see it against the pale background, is that we have to review the budgets of each approved application for any changes that were approved, for arithmetic

errors, and to screen unallowable charges as defined in the original RFA. We now have completed this task and have precise final budgets for each approved application.

- the second task, we need to find a way to make the approved payments. And at present we're developing a procedure with the state controller's office so that the state can transfer the appropriate funds to each grantee in a responsible and in a traceable and trackable manner. and
- third, we have to make sure that each grantee or recipient understands our, the CIRM, the principles of operation as well as their roles and responsibilities when they choose to accept an award from the CIRM. and that leads us to the purpose of a grants administration policy or a gap, g-a-p in short.

GAP Contents.

- The policy statement will set out terms and conditions of grant awards from the CIRM.
- It will tell recipients what are their responsibilities as grantees. And this information will be directed at recipient institutions; that is, officials authorized to represent the institutions as well as the principal investigators or PI's. and
- finally, recipient institutions and PI's must then agree to comply with these conditions and procedures before they can receive funds from CIRM. So what's covered in such a policy statement? the contents will include information that will be useful to grantees and applications, such as who are the CIRM staff members that the grantees are likely to interact with and what are their functions? What are the eligibility requirements for institutions and PI's? It will provide general information on submitting an application, how applications are reviewed, and how are they approved for funding. the grants administration policy will spell out terms and conditions of the award, including issues of rebudgeting. What if the PI moves to another institution or even out of state? The CIRM policy on intellectual property that you heard that's currently being developed by the IP task force will be included. Policies on sharing research data, technologies, and materials policies that would be approved eventually by the ICOC will also be included. Procedures for annual reports on scientific progress and budgets so that we can follow what's going on, how the grantees spent the money.
- the policy statement will include CIRM requirements and standards on matters such as use of human stem cells, use of vertebrate animals, use of biohazardous materials and human subjects. And then we will be stating in the policy statement CIRM requirements and standards that you provide for us and that will eventually be approved by the ICOC. These include use of human stem cells, vertebrate animals, biohazardous materials, and human subjects.

Policy development

- Earlier in the year CIRM contracted the firm LMI to identify and compare policies used by a number of public and private grant-making agencies, including the American Cancer Society, Juvenile Diabetes Research Foundation, the California Special Research Programs for breast cancer, tobacco, and AIDS, American Heart Association, and the NIH.
- LMI's comprehensive report covered a very long list of topics including types of support, roles and responsibilities of organizational staff, public policy requirements, and intellectual property. They also provided us with information on procedures such as how different agencies notified the successful applicants and their particular reporting requirements.
- we then had a CIRM team that has been meeting regularly to develop a first draft of an interim grants administration policy statement. We developed a draft of the interim CIRM grants administration policy for training grants. Now, the training grants was a priority because with the board's approval, we needed to be to ready to award these applications as soon as possible.

- This first draft of the training grants administration policy was posted on the CIRM website, presented to the ICOC on November 2d so that the board is aware of the progress of this document. The scientific and medical research funding working group, who reviewed grants, also met by teleconference on November 28th to review this draft. They recommended approval of this document with two amendments which are the length of time that medical students could spend in order to fulfill clinical duties that are outside of the scope of research. They are argued for a 25-percent cap, and that's been added to the amended document. And also standards for reporting IRB, ESCRO, etc., that's needed, and that's the last section in the report. e intend to present this amended document to the ICOC on December 6th for their discussion and approval so that the training grants can be awarded in a timely fashion when funds become available.
- coming back to a slide that you have seen earlier today with the IP presentation, you can see that there are multiple inputs that come together in order to form a policy to enable us to fund the training grants. The multiple inputs are the interim IP policy for training grants, this particular training grant administration policy, as well as the interim ethical standards that this working group has come up with. So you can see that it's important to have good communications between the working groups and the task force over issues of shared interest.
- this process is just the first in a series of steps in order to get a final product which is a comprehensive grants administration policy and regulations for all research awards in general. And so in that piece that you see below, the general IP policy, which is going to be hammered out, looks like in the spring, plus the ethical standards coming from this working group will all come together for the final comprehensive policy which will be adopted pursuant to the California Administrative Procedure Act.

Lo: The first question is the timing of ESCRO review by the institution that's applying for funding and the timing of grant review by CIRM? We've thought about both options, first requiring that the ESCRO approve a proposal before it's submitted to CIRM versus the obverse, which is the NIH system of once you get funding, then you need to have IRB -- only then are you required to go get IRB approval. So that's the first issue of timing of in-house ESCRO reviews versus CIRM grant review. second is the issue is of enforcement.

Chiu: The argument for pre is that you weed out grants that ESCRO has deemed unethical or not appropriate standards. And then there will be less grants for the grant review group to have to go through. The grant review group's task is to assess both scientific and programmatic excellence, and they depend on local IRB, ESCRO, etc., to determine whether ethical standards and local standards have been adhered to. the argument for having it done afterward is that it doesn't stop researchers from submitting a very exciting application. And if the RFA doesn't give them ample time to not only craft the application, but also to get all their ducks in order in terms of all approvals, they cannot submit an application in time by the due date, right. So there are on the two tensions. if you want to the RFA's to move in an expeditious manner and get everything reviewed and funded, then to know that you're going to get funded, you would want to have a fast track after the fact. Only approved applications will to be asked to have what's known as closing package, which is to have all your ducks lined up before you actually trigger the funding, the award process. the preprocess, researchers would argue that it takes them a long time, it might even prevent them from reviewing. So we have not going to the working group to iron out this particular issue. We will be presenting it to them as two options. The thought is that if we offer the closing package option, it would be a burden on the reviewing group to review all grants whether they have ESCRO approval or not. On the other hand, it will allow researchers to be able to submit grants quickly and would not hold up the whole batch. and not every application may have such onerous -- such extensive ESCRO review. Also, it holds the applications hostage by the ESCRO and the IRB reviews. money will not go out unless those are approved, and that would delay funding. At

least only those applications that are deemed scientifically and programmatically meritorious will have to go through their internal review. a final thought was that sometimes during review, the reviewers put in comments and recommendations such as we would like to see this eliminated and that element added. That might change the ESCRO review process or considerations for ESCRO. and that could be included if it's a post activity. So to cut a long story short, it may be that we would ask in general for this information, the approvals to be provided, after an application has been approved for -- deemed appropriate for funding, but that under certain special circumstances particular RFA's we may request it beforehand as special conditions.

Lo: It's important for us to know how the grants working group is thinking on this issue. We certainly don't want to do anything that runs counter to what you're thinking. second question for you had to do with violations of CIRM policies and enforcement mechanisms. as we were thinking about what might happen or what ought to happen if a CIRM-funded institution or researcher doesn't comply with certain things. Has the grants administration working group thought about this? and do you have thoughts as to whether penalties might go beyond just suspending or withholding the remainder of the grant to disqualification from applying for future funding, for example?

Chiu: so this element of implementation and checking for violations and consequences we have not brought in front of the working group. But all I can do is address some ways of dealing with it that I've seen from other agencies. And as you said, withholding of funds is the easiest and the most directly felt way and most targeted to the individual that violated the program, but that's after the fact. usually at about the time of the progress report when you review and for program directors to go in and call about specific activities or if you hear about specific violations from people reporting on it, a broader consequence may be, and I'm just saying may be, has not been discussed -- it's just bringing it to your attention -- might be some period of prohibition for that individual to apply for CIRM applications. And a much more severe one that the NIH threatens and with great effect is to withhold all funding from a particular institution until a certain violation has been corrected. This will happen, say, if the animal quarters are all grants are affected, for example. but we have not discussed this particular issue of implementation and severe consequences yet.

Cibelli: When will the funds will be available for release. What's the legal situation at the moment?

Hall: There was a hearing on the 17th of November of the two suits that have now been combined, which challenge our constitutionality. Basically they say we are giving out the state's money, but we're not a state agency. And so that prevents us from raising money in the bond market. and we just heard yesterday that all except a small portion of those suits have been dismissed. there will be a meeting next week to discuss the schedule and then a trial, we suspect, sometime in the spring to discuss those issues. James, maybe you want to comment on that little more expertly than I just did.

Harrison: In essence, though the court found in the CIRM's favor on several of the different legal theories the plaintiffs have advanced in support of their argument, that proposition 71 is unconstitutional, she concluded that she couldn't grant judgment in our favor at this time because, in her view, several of the claims, three of them, require further development before we she can reach a conclusion as to those claims. And what that means as a practical matter is at the case management conference that she scheduled for next Tuesday, we'll have an opportunity to talk about the scope of the issues that remain, what discovery, if any, is necessary in order to resolve those issues, and when we can set a hearing date to bring it to closure. the one additional positive aspect about the court's ruling is that she recognized that this action is entitled to preference on the court's calendar, and she expressed a desire to bring it to that hearing and to a conclusion promptly. So we're hopeful that we can continue to push this forward as quickly as possible to get to a resolution in the trial court.

Cibelli: If it were the case -- I'm assuming this is going to go back and forth several times. So that means that the funds will be stranded until when?

Harrison: You're correct, that there are different stages in the litigation. We're hopeful to get through this first stage in the trial court sometime in the spring, and the earlier, the better; but obviously if we're successful, the plaintiffs will have an opportunity to appeal. And that will continue to have an effect on the state's ability to market the bonds. A positive ruling and, in fact, even the ruling that the court issued this week, which does indicate that the court feels that several of the plaintiff's claims lack merit, does help us in terms of convincing potential purchasers of bond anticipation notes that their of risk not being repaid is minimal. so I think we have made some progress. unfortunately we still have a ways to go until we can ultimately reach the end of the road, which is a final judgment with all appeals exhausted.

Hall: We are trying raise bridge funding; and while I think we have positive results in that area, we have not reached conclusion, and we are hopeful that shortly after the first of the year, we will have some money that will allow us to at least to fund the training grants.

Rowley: How much is the total for the 16 training grants approved?

Chiu: $12.1 million for the first year of training, and a total of almost $38 million to fully fund the three years.

Taylor: I think I'm in agreement, but I'm just sort of curious as to a priori, the training grant, was that component set out as the most important first step with obviously the first 12 million that you can raise, not that I -- I was just sort of curious as to what the thinking was.

Hall: There are two reasons for that. we decided to issue that RFA early on. One was that we saw the training of stem cell researchers as a clear and urgent need for the entire project and one that was a sort of long-term investment. There will be an enormous expansion of stem cell research in the state as a result of this. That will take a large increase in manpower. And so also our sense had been that because of federal policy, a lot of young people were avoiding this area because of the uncertainty in funding down the line, so we wanted to send a loud and clear signal. and the other is a more practical matter, and that is that we wanted to get our grant-making activity started as quickly as possible. It was at a time when our staff was very limited. We were just putting together our grants working group, our procedures were unclear, we're still working these things out, and we thought that if we put out a call for research grants, we would get probably hundreds of applications and would be overwhelmed. But we received, I think, in the end 26 applications, if I'm not mistaken. This is a manageable number. Actually it worked out very well, so we were able to walk through the procedures, and we were very pleased with the way that came out. We have, we think, an excellent training program once we have the funds. and I will say that the procedures also present some challenges for us. The final decision is made in a public meeting, for example, by our board, which is unusual for the kinds of process that we're used to rather than with the NIH. And so to manage the different steps of the process and to do it in accordance with both state law and to have a maximum possible transparency while maintaining confidentiality was a bit of a challenge for us. We were able to work through how we did that on a relatively small scale, as I say, without having to handle extremely large numbers of grants. So it was a very good way for us to get going. We have the training program in place. Also, I think it's, in retrospect, a modest amount of money given our difficulties. If we had to raise 200 million, let's say, to fund a broad research program, I think that's much more difficult than this. so it was both a substantive and scientific rationale and a practical rationale for doing it in that way.

Taylor: It's hard to know whether you should build automobiles first or petroleum processing plant, but I think it was a good decision.

Hall: Modern version of the chicken or the egg.

Lo: I want to sort of shift gears a little bit and move on to some issues that are different than the consent issues we've been discussing, or somewhat different at least. I think we've had a very rich and very productive and very useful discussion. Given we have a lot of things for staff to kind of translate into regulatory language, which I think we'll try and do before our next meeting, there's another set of issues that really have to do with three different categories of research you might fund. we set out here three different broad categories of research.

- One is stem cells derived with CIRM funding after this policy goes into effect.
- B is stem cells derived without CIRM funding, but after the effective day of this policy. what are the minimal Requirements that we want to have for those cell lines, Taking into account all the practical difficulties of finding out a lot of the details if they're derived Under somebody else's auspices. The challenge here is to find out what are the things that we would want as sort of minimal requirements so that if there was noncompliance, we would not allow CIRM funds to be used for research with those lines.
- The third category is going backwards even more in time, the grand parenting issue. This would involve NIH stem cell lines, for example, where they may not meet the criteria that are set out in a or b. They were derived some time ago, but they're scientifically important. And since they're already in existence, should we allow CIRM funds to be used for research with them? Included in our briefing were some materials from the department of health and human Services, which are the federal guidelines for if something is derived without federal funding and doesn't need to fall under federal regulations, what are the sort of equivalent protections you would want to have in place to deem them acceptable for funding?

Some of the things that have been suggested were that it has some sort of IRB and/or ESCRO approval. It strikes me something about consent, which actually isn't under b (1) here, but free and voluntary consent, I think we'd want this perhaps. Without payment beyond reimbursement, again to be consistent with prop 71 and given our discussion today, would we want to say without any restrictions placed on future downstream scientific uses?

Eggan: Can we see that language from the CIRM legislation it certainly says that CIRM research dollars can't be used for research involving derivation, which includes compensation, but does it speak to outside cell lines specifically?

Harrison: It does not specifically speak to that. The language, as I read it, it simply says standards prohibiting compensation to research donors or participants while permitting reimbursement of expenses. It's not specifically addressed.

Eggan: I think this is a big deal. I think there may be other groups which decide it's reasonable to, say, compensate for lost time and may make very valuable reagents that CIRM researchers may want to use. I see this as a difference in opinion.

Hall: I think it was stated before that this is an issue in which a very thoughtful and considered case can be made on both sides of this issue. I would like to ask the working group to at least consider the possibility of whether it might not acknowledge that there may be an honest difference of opinion by other groups on this issue, and that to categorically rule out the use of those cell lines by California researchers might not be a mistake.

Kiessling: The most important consideration is whether they had fully informed consent and that they knew exactly what they were doing. I think the issue of compensation should be informed and voluntary. I think how the donors were recruited and how they were treated during and after, I think that is a far bigger issue and far more important than whether or not they were compensated.
Secondly, I think it's really important to not substitute the term "out of pocket." I think that should not appear because that's not what the statute says.

Prieto: I agree that that seems to restrict us unnecessarily and rather just go back to the original language of reimbursement of expenses.

Eggan: This is maybe even more limiting than we need to be because the legislation may say that we cannot derive cell lines except under these conditions, but it doesn't speak to cell lines derived outside.

Prieto: James, does the initiative actually specifically refer to derivation?

Harrison: No. What the act prohibits is CIRM compensation of donors for anything other than reimbursement of expenses. So we're really talking about CIRM funding to the donors as the limitation.

Eggan: One can consider a situation where CIRM funds derivation, but from other funds from that research group come the funds for compensation.

Hall: Consider the issue of the use of lines derived elsewhere where compensation is permitted. I think that's the first issue to really have a clear, policy on whether to say we want to apply this standard to all or to say that we recognize there may be a difference.

Eggan: I think the first is a loophole we want to close, and the second one is a loophole that we probably want to leave open, at least in my opinion.

Taylor: For this one it seems that the voluntary informed consent should be enough. It doesn't seem to me it needs to be a priority listed in our criteria for acceptance. I think that previous cell lines, if they were derived under appropriate informed consent, could be eligible and with no discussion of compensation.

Hall: In the future will we take cell lines, and then we'll deal with the others later.
Feit: for those of you that are with working stem cell lines, obviously you worked with them before this point in time that prop 71 came along. I'm assuming that you applied maybe the academy guidelines to your cell lines or you had standards that you used?

Eggan: I can certainly tell you that in, Doug Melton's laboratory; there have been issues, just how broad is broad enough with respect to informed consent? I think there needs to be some sort of understanding, that there are differences of opinions. As long as there was free and informed consent, then I think that we may want to let some things go by in order to enable the science.

Lo: Let's distinguish lines that are going to be derived after our regulations go in effect, which is what I'd like to talk about first.

Eggan: It's going to continue to be a moving target even after.

Kiessling: I think the answer to Marcy's question is that the technology for deriving stem cells from egg donors is new. What Kevin is talking about are cells that are derived from frozen embryos. So the egg donor issues are brand new.

Hall: In actually historical fact, proposition 71 included the no compensation. The national academy guidelines appeared only last April, and they adopted a standard that was in proposition They made conscious reference to the fact that it had been first in proposition 71.

Secondly, the national academy guidelines have only been in effect since April. I think right now, just to emphasize the point, we're talking about ones that might be derived in the future.

Cibelli: There are two things here. One is to ask the question whether the cell lines were derived after IRB approval, independent IRB approval. The thing that is a little bit more difficult is to judge how was the consent form made. And I wonder for us it would be too hard to judge that because there are not too many cell lines derived by in this case somatic cell nuclear transfer that will come to California. So if we can look at the consent form and decide that it's not a consent form, it's just a joke, we shouldn't allow those cell lines to be sponsored by CIRM. And if we think that those consent for are appropriate, we should go forward.

Hall: It's not just egg donors as we're talking here, but also embryo donors.

Cibelli: So you have a handful of clinics around the world. We have a couple in Israel, we have Spain, Australia, you may have Singapore, the UK, so there are not too many. I think this is going to be our role just to make sure that if you are going to approve that, if you are going -- this will be a nice place where we can be very, very vulnerable. We should be the ones looking for the consent form.

Hall: Whatever we put here will become a California regulation, and it will be very, very difficult to change. So what we want to do is set out procedures that will guide whatever decisions are made. I think what we don't want to do is to have specific approvals here.

Cibelli: What I'm saying is let's say there are 30 different laboratories around the world and they have cell lines already circulating around, and people from California wants to use those cell lines. All we have to do is send us the consent forms.

Hall: I don't think we want to do that. What we want to do is to say to the ESCRO's that they must be assured that the following principles have been followed. That's what I think this -- to put into this regulation, that's what we need to do.

Cibelli: You realize that every single country will have a different way of doing things.

Hall: We need to establish the principles and to say what it is we'll accept, and then the ESCRO's will have to enforce that.

Eggan: Unless we could say that CIRM-funded research can only be conducted on embryonic stem cell lines which are deposited in the CIRM stem cell bank. And only CIRM bank lines will have been approved by this or some other group that we approve of, right. That would certainly live up to the model that Jose was just saying.

Hall: Yes. The problem is that's also a moving target. We will have to have plans for the bank, set it up, and be sure that it's in existence. Otherwise, nobody can use these things until we set the bank up. That's not what we want.

Lo: Section a, I think that's not going to be as controversial because we get to call the shots with things we fund. So (a) is stem cells derived with CIRM funding after the effective day of this policy.

Hall: let me just ask isn't (a) what we've been talking about most of the day? And that will be redone in accordance with -- that will be redone in accordance with all the discussion we've had up to now, so we don't need to do that.

Lo: (b) and (c) we haven't talked about today, and I think I'd like to have that discussion.

Lomax: Just so folks are clear on the origins of what we are working off of, (a) is essentially taking what was in the national academies guidelines, and those sets of conditions that were appropriate for the revised framework were dropped in. So (2), (3), and (4) are essentially the raw material from the national academies' guidelines. And correct, we now need to update this section based on today's deliberations.

Lo: let's talk about (b) for a minute. First would be IRB oversight or from an equivalent body to an IRB.

Lo: Let's go through everything but payment, but let's see if we can at least agree on the other ones. So IRB oversight, any concerns about -- anyone not want to have that as one of our core criteria? I think we have to. Second, which isn't in here, and I think probably should be is free and voluntary consent from the donors.

Prieto: and the wording that Ann mentioned, fully informed, free, voluntary, and fully informed consent.

Cibelli: You consider the consent firm should be made available upon CIRM request or something of that nature.

Hall: I think Ann's point was that it's not just the form. It's the whole process that needs to be acceptable.

Lo: If we get the concept that informed and free or voluntary consent are essential, and then craft the language, let us have staff work on that and come back to us. Jose's point is we have to have access to information.

Cibelli: You don't want to find out a year later you were paying for something that was obtained unethically.

Lo: Without consent. Should we require that if CIRM researchers are going to be funded to work with, there should be no restrictions on the downstream use of the cells? No.

Eggan: I don't think so. I think the language explicitly was used to try to preclude future anonymous gamete donors, which is one of the problems in the past. Almost certainly we're ending up grandfathering in cell lines that were probably derived using some anonymous gamete donors. In my opinion I think we want to move to preventing the use of those types of cell lines in the future. So that should be explicitly stated.

Kiessling: Under the fully informed consent.

Lo: I guess the concern is, we talked earlier this morning, about how if we're deriving under CIRM funding, we'd like the lines to be available for all kinds of uses that we may not anticipate. So we would not want CIRM funding to be used to derive lines or the donor put restrictions on future uses

Eggan: I think there might have been a misunderstanding. I think what we want to avoid is in a single study to have certain donor line item vetoing certain things that could be done. I think that's very important so that within a particular study which was prescribed for a particular purpose, that you have different classes of embryos within that one particular study. I think that makes for an impossible situation. But there may be cases where one derives a line or one has embryos donated for specific things which are prescribed. I think there was language which said that the donor should have the ability to be able to rule out any particular use of a particular cell line that's derived within a study. [in this scenario] you have to track every single document that was used for that study, and that's where things become impossible.

Hall: That's not an issue, is it, for lines derived elsewhere?

Eggan: No. But the language, as stated before [suggested this]. That's where I was raising the objection.

Lo: I hear that we want to remove that suggestion.

Kiessling: I'm not sure everybody understands. I think that CIRM funding should not be used for lines that have restrictions. I think that's too complicated. I don't know how you're going to track it, and I think it's a huge problem.

Hall: Wait. Lines that we derive or somebody else derives?

Kiessling: Somebody else derives. I don't know that you want to spend money on a line that can only be used for Type 1 diabetes research.

Hall: Supposing an investigator comes up and they have some very specific question they want to answer? It's not dealing with a particular restricted use. Should we say you can't do that because there are uses that are restricted?

Taylor: I think that all the lines should be in a CIRM bank. I think that lines that CIRM investigators have access to within CIRM funding should be done under sort of the CIRM umbrella. I actually think that it's a nice idea to have those be carte blanche lines that don't require complicated tracking. Now, that's going to limit the number, but I still think that pragmatically it's going to be easier going forward with that. I think that if you fund one CIRM investigator to do one set of experiments in a line that can't be used in other ways.

Hall: I'm just reluctant to put that restriction on not knowing. I think if at the time it comes up and is reviewed, if somebody has a grant, I think you need to look at it on its own merits. I would be very reluctant to put a blanket restriction on that. I think the other point is stem cell bank, if we have to have all lines that are used by CIRM investigators for whatever purposes are in our bank; this is going to be a big requirement. It's going to take time to get that bank going. I think it's going to be a big issues how we do it, and I think that, again, is unnecessarily restrictive. I would like to leave that open.

Prieto: When you have very well characterized ethically derived lines from the UK stem cell bank, for example, and I think we would want to fund research on those lines, and they may not want to put to cell lines --

Hall: We probably would end up with a reciprocal relationship with them in some ways that we would share between our banks, but we wouldn't necessarily bank and characterize every line.

Feit: Didn't you say earlier that the ESCRO would be responsible for complying with any restrictions on the stem cell line? Is that what I heard earlier?

Hall: Yes. I think if somebody were to apply for a grant, then it would be to use a stem cell line in a certain way, then it would be up to their ESCRO committee to be sure that they weren't violating a restriction on that line. We could not be responsible for that.

Feit: Isn't that what we, in fact, should put in there, so that leaves it broad, that we leave up to that body of people to follow any restriction that may be attached to a stem cell line?

Hall: Yes. That goes without saying. What I'm objecting to is to say that if a line has any restrictions on it all, it can't be used for anything… [unintelligible]

Lo: As I understand it, the point is that you don't want to put that as a blank prohibition because someone may submit a very meritorious grant that uses a very restricted line to answer an important question. You don't want that precluded automatically by this restriction, but there's nothing to prevent a grants review team from saying, given everything else, why aren't they using a stem cell line that doesn't have restrictions.

Prieto: I think that things will come to the grants working group, grant proposals with lines that have lots of restrictions, and they may get turned down for that reason.

Eggan: I think it's a very different thing altogether to actively encourage or to force people with CIRM funding when they derive new lines, except for some extenuating circumstances, to require that they do so under informed consent that would allow general use of those lines.

Lo: Which is what we talked about this morning. I heard before a lot of people saying that they don't want to apply CIRM restrictions on payment for time beyond out-of-pocket expenses to lines derived with other funding. It's very hard to know what you're paying for when you write a check to someone who donates oocytes. I mean paying for time somehow seems different from saying we're buying the oocytes. Let me just put this in context. The first Ortiz bill, which is several years old, had a prohibition on purchasing or selling embryonic cadaveric or fetal tissue for research purposes. Now, we're technically exempt from that under prop 71. I think there's a lot of sentiment related to buying and selling oocytes, which it's hard sometimes to draw the line between paying for people for their time it takes to go through an extensive counseling, education, and manipulation process. But do we want to say if we're not -- and I didn't hear a lot of support for prohibiting payment for time. Do we want to say that paying for time may be permissible, but paying for oocytes outright is not, to the extent that that line can be drawn? So we draw the line elsewhere in research or at least try to.

Cibelli: This is something that we are going to have to live with. Unfortunately proposition 71 had that clause in, but I thought actually that when the Koreans announced that they have done all this nuclear transfer experiment with donated eggs, I thought that maybe we could learn something from Korean women. But the truth is that those were compensated. Nobody really knows what's going on right now.

Hall: I thought that had a series of procedures that had been put in place after the first paper and before the second, and they had quite an extensive procedure, which, as I recall, had several layers of counseling. It was, I thought, in many ways an admirable procedure. I can't say that that's what they followed, but my understanding is all the controversy has been about procedures that were done for the 2004 paper that involves one cell line. As far as I know, there's been no controversy over the 2005 paper. That's not to say there may not be, but I just want to make that record, make that point clearly.

Eggan: Again, I would say, yes, that's my understanding as well, but would echo what Jose said. And we'll wonder and see. And I think that this is probably something that we should make a statement on.

Cibelli: I would argue that we have to compensate, we have to find a way to compensate, and you can very easily put a cap on it and just say this is the amount of expenses that going to be reimbursed, period. Otherwise, you are going to have a very hard time finding women willing to help out.

Prieto: We can't call it compensation. We may have a little bit of latitude in terms of how to define expenses, but that's all the latitude we have. This is talking about outside lines, and the question is do we accept other people's compensation, money that we did not provide?

Hall: It's an interesting question. Ann raised the point of the very well-established clinic in Britain that requires that anybody who goes through fertility treatment there donate a certain number of eggs. Is that for payment or would we refuse those lines?

Prieto: Are any cell lines derived from that in the UK bank?

Kiessling: I would guess yes.

Hall: We don't know.

Prieto: Do we consider those to be ethically derived and cells that we would fund research on?

Hall: What I would argue for is to somehow have a more nuanced consideration of the conditions under which consent was given to get to the core issues here. Maybe compensation isn't the most important issue, but it's a number of other issues that we specify.

Kiessling: I think it would be valuable to this conversation to go through a like a briefing I did to the Massachusetts legislature when they were looking at their deriving their stem cell law. And the women legislators had a caucus, and this caucus had received information from some women's groups that were very concerned about the exploitation of women with respect to this donor egg issue. And I understand those concerns.

I also have a very strong feeling that women really have the ability to make decisions. The women's caucus in this group, their concerns about compensation were twofold. And I think that's why there's information in proposition 71 about this.

You don't want to exploit anyone. The idea is that somehow you must protect women from putting themselves at risk to make money. There's lots of ways to do that besides talking about simply not paying them at all. The women were mostly black and their concerns were several-fold, that women from their communities would be recruited to donate eggs for large sums of money, and that the stem cells derived from those eggs would not go back into their communities. So they could see themselves being exploited to the expense of wealthy people. When I went through what the consenting process is about, what you do to educate somebody about what the eggs are going to be used for, how this is going to work, within about an hour that same group of women from the black community decided why should we limit the ability of women who want to be egg donors to make some money. So they went from not being worried about compensating women to be worried about restricting the rights of women to actually receive compensation for this effort.

I really think the idea behind compensating egg donors for this research needs to be left alone for a while because I think the more people think about it, the more they realize that's not the important point.

The important point is [not] whether she's compensated or not. The important point is that she really understands what she's doing, that she fully understands the risks to her, how long it's going to take her, the short-term risks, the long-term risks, and what's going to happen to the cell lines. And whether she is compensated for the time it takes her to do that or not is irrelevant.
I think that in the consenting process itself, you cannot establish guidelines for people in Singapore or other parts of the world that may actually view this as a way for women to get together and actually create a small business to donate eggs. I don't think that should be absolutely prevented. What you want to prevent is having somebody go through this procedure that was not fully informed and not doing it of their own free will.

Peters: I'm trying to respond to the question about what's the core matter. So what is the philosophical principle that we're trying to honor here as we formulate our ethical mandate? Is that it that we shouldn't treat something that is distinctively human as merchandise that can be bought or sold? Is that what it is? If so, then we could minimally say that you can't purchase oocytes and they cannot be sold. Is it to avoid the exploitation of women? Then given the complexities that Ann just announced, and then we would get in the business of deciding what a fair price is. I'm not sure we want to do that. So what it is that we're trying to respond to that this policy should be formulated to honor and respect?

Hall: I think Ann brought up an interesting point, but I just want to underline. By taking the compensation stand that's in here, one could argue that it makes it much more difficult for poor women to be involved in these activities than would otherwise be the case. I think that's something that deserves real consideration.

Cibelli: I think our mandate is to move this research as fast as possible without putting anybody at risk.

Taylor: I feel that the law as it's written in prop 71 at this point is relatively immutable, which makes me believe, and this isn't to cast any aspersion I think that what we're discussing now could easily be interpreted as a complete loophole to move stem cell derivation out of CIRM into an organization next door that would then just feed stem cells into CIRM. If that's what we want to do, then this seems to be the way to go to do that. That's sort of a dark interpretation, but what's to say, then, if we say that we will accept stem cells derived after the prop 71, independent of compensation, coming into CIRM, then what it means is that investigators within CIRM won't be able to compensate donors for stem cell derivation. It's just that you will have created another service outside of CIRM that will compensate their donors, which I think most of us believe should occur, and then the stem cells would end up back in CIRM through the back door.

Hall: We certainly would not do--that could be arguably an indirect consequence of this, but I don't think people are going to set up to supply CIRM with cell lines through some circuitous thing. We almost certainly will put money in California into the derivation of cell lines and my guess is we'll put substantial sum into that.

Taylor: If there's not money for the donors, and I think most of us believe that they're not going to be--

Hall: You think there won't be donors without money? I think people are going to do this according to a variety of ways. Already we've heard a number of different ways people are going to be doing it anyhow, and they're not going to be doing it with an eye to the California market. If it turns out to be really difficult to get people to do this, or maybe people will have overriding concerns about who can afford to do this, this demographics of the donors under these conditions, and they may come to the conclusion that they want to do it a different way. I think that's what's going to happen. So the question is do we want to exclude cell lines that are made by well-meaning, thoughtful, responsible people who happen to come to

a different conclusion for whatever reasons than we do on this particular issue? That's why I was pushing for the core issue.

Kiessling: Whether or not you pay women to do this is going to be irrelevant to how many volunteer. You're not going to have to compensate women in California or they won't come forward. That's not true. Lots and lots of women are going to be willing to do this. It's going to be a select group. You are not going to recruit people who can't afford to take off two weeks to do it. So all you are doing is shifting the population of women who are going to be able to participate. You're not going to restrict it. There's going to be plenty of women who are going to volunteer to donate eggs because women do things like that. The problem is whether you ought to accept lines from other parts of the world or other parts of the country that have different guidelines. So this is not going to be a restriction in California.

Feit: I think my concern would be you said there's a cell bank in Singapore. What assurances do we have that even if we get paperwork that says informed consent was given, how do we validate the process of informed consent? Many times cultures work under different understandings of processes than we do. I think we have to give really careful consideration to lines that were derived before our standards were established. And I'm not saying I have the answer of how we're going to go about that because I hear the plea from the scientists that you really want to include as many lines as possible that are usable for research. But given that, the attack on CIRM would be vicious internationally if we accepted one cell line that wasn't properly handled in another country. To validate that process, to really understand, as much discussion as we had this morning regarding protecting women, and we know what we want, how do we validate that with cell lines that were
created prior to this understanding this morning?

Lo: We're right now talking about cell lines created afterwards, the grandfathering, the section we haven't gone to yet.

Hall: I think we should all understand there's a tremendous international effort to make sure that all this is done ethically, and there are groups cooperating in Britain, in Sweden and Israel. There's an international stem cell forum. I think the example of the Koreans is going to be a very salutary one for anybody in this area. So I think there will be intense pressure within the community to have stem cell lines derived according to a high ethical standard and to cooperate so that we will end up knowing quite a bit actually about what goes on in other countries, and there may be odd places that spring up here and there. I think we will need to take the kind of care that you described, Marcy. I think the real issue, and I think this is in a way that issue with the Koreans, I think you
can't -- it's not our business in a way to go in and examine specific cases. If a cell line comes up, who gave the oocytes and who they were, all of that we do not want to get into. What we want to be sure is that there is a good regulatory process comparable to our own, at least in broad outline, that oversaw that process and that checked it out. If we can't validate that, then I think we can't accept lines from that system. I think that's the way we have to operate and to figure out a way to incorporate into what we do.

Prieto: I think Zach is right, that there is a lot of oversight and scrutiny of this, and it is around the world, not just in California. And the example of Korea is a good one. No one will be able to keep secrets. If people are doing things in a way that would not pass muster, that's going to come out.

Lo: I want to have us think through a little bit sort of what the concerns are about payment. Ann very eloquently, I thought, explained one concern, which is that if you have payment that's an undue inducement and women really haven't gone through a full informed and voluntary consent process, there's the risk of exploitation, and people are doing things and not realizing what the risks and consequences are. There are other concerns about payment in research, and Ted alluded to one which I think is really quite salient in the minds of some people on this topic. That's the issue of putting a dollar

sign on things that some people believe shouldn't have a dollar sign, should be bought and sold. Just as we do not allow solid organs to be bought and sold overtly, there are some people who think that certain things should be beyond purchase. Now, how do we draw the line between paying for the oocytes as opposed to paying the woman for the time she put in?

Paying her for out-of-pocket expenses is an iffy line. But as an example, when Ann calculates out the total amount of dollars that an oocyte donor gets in her program for going through this very detailed process, it's 10, $20,000 probably, but the going rate for oocytes on the open market is a lot different. Suppose a researcher is saying I'm going to pay $50,000 because I know I will get oocytes and a lot of people step forward. Is there some concern that that's beyond paying for time, and it's really somehow paying for the oocytes? And is that a concern that somehow putting that amount of dollar on the oocyte somehow violates people's concerns about some things ought to be non commodifiable?

Hall: Was the 20, $25,000 figure that you used, what was that?

Kiessling: An egg donor cycles is like an IVF cycle, although it's a little more expensive. About $20,000 a cycle.

Lo: The compensation to the donor --

Kiessling: Is tiny. It depends on how much they do. If they go through a full cycle, they spend about a hundred hours and we cover child care too, so it comes out to about $4,000.

Lo: That's calculated on the basis of expenses. But there are other people who might say why stop at four. You can get more donors for 10 or 20. At that point are you really paying for the oocyte?

Cibelli: I think our mandate is to move the research forward fast without putting anybody at risk. So if the consent form explained the risks and the women are free will of what they're getting into, doesn't matter how much you pay them.

Peters: Bernie, I think that what you're formulating right now is the center of the issue. And it applies both to what we're going to fund and what we're going to accept.

Is that the public is outraged at these ads in college newspapers for women to donate these eggs and to get lots of money. Part of being ethical whether, we like it or not, is to be responsive to the culture around us. I think people would expect from prop 71 to reduce the outrage so that somehow or other the standards that we set should not encourage this kind of use of money for the buying of parts of human bodies and stuff like that. Or Leon Kass calls it the wisdom of repugnance. There is something here to this.

One of the things we can't do from our vantage point in proposition 71 is regulate all this. We can't do that. Could we maybe do a minimalist kind of thing, simply articulate a principle that says you do not buy oocytes or embryos or something like that, and then just leave it at that? The way that's going to get interpreted will be in multiple ways, but I think that at least we will have spoken to the question of yuck or the wisdom of repugnance or the protection of human dignity, which is really what's at stake.

Eggan: We need to protect human dignity. I couldn't agree more. But I find the wisdom of repugnance not terribly wise because there are many things which we as a society once found repugnant, but now widely accept. This is one area where, at least personally, I have a great departure from that point of view. Society is dynamic and is ever changing, I think that we should try to intuit our way through the

yuck factor and figure out what it is about these things that make us uncomfortable and is or is not right. So but then again, I also think that Bernie's statement is taken in good spirit.

There are certain expectations in society that we couldn't commodify certain parts of our body. The problem here is that, again, as a I said earlier, that eggs somehow lie somewhere between blood and sperm and a kidney. And so I think this is a difficult thing. There's not -- I think it's fairly clear that we should not in any way encourage people to be paid for something which they can never get back, like a kidney. So to dissociate that sort of donation from monetary reimbursement is important. I think the risks are less clear here than they are in that sort of situation.

Lo: Again, we can't vote because we don't have a quorum, but I'm hearing a lot of different views.

Sheehy: A couple of points. First of all, people are selling eggs into IVF clinics. And I haven't heard the outrage. I think if you talk to a parent who has a child from that, I think that you have a completely opposite reaction from outrage. I don't see that that practice will stop as long as people are able to have kids through that method. I think that's where a certain balance has been achieved where people say look at this kid. I don't object to the fact that someone paid a woman to make a donation so that this kid could exist.

The other point is I'd be very careful about Ted's point about not buying embryos. It's one thing to be talking about whether or not you're compensating a donor, but actually there is going to be a market in this, but it's going to be third party. A fertility clinic is not give this away. There are costs associated with storing, moving, distributing. We want to pretend like that there's not already a market in these things. Only thing is what we're arguing about is whether or not the person who actually gives the very first product gets anything. But everybody else up and down the line is getting something. So you can say that embryos won't be for sale; but when someone gets an left-over embryo, they're not given away by the fertility clinic. They don't say, oh, here take it. There's some cost, and that cost includes something that even within a strict cost when they make a strict cost. There's some element of that that's profit for somebody, so I think we have to be very careful about this.

Peters: Two points. I think you're right, that this proliferation of activity and people getting a cut of the profit, that's going to go on. I don't think we could control that. We probably can't even guide it. So that's why I'm floating this idea of just a minimalist statement that these parts of the human body cannot be bought or sold. I think Kevin is right in raising the question: what is this -- where is the closest analog? Is it like a liver, or is it like hair and fingernails or something like that? I think its like -- it's like a human organ. Why? Well, because of the risks to the health of the woman in the process. So that was what tips me on the side of wanting to treat it more like an organ rather than treating it as something that is easily expendable. We ought to decide what are these oocytes like? Are they like organs or they're really like getting a haircut?

Sheehy: Why do you make a distinction between an egg and sperm?

Peters: Because I think there's a large risk to egg donation that isn't there for a sperm.

Sheehy: Not if it's a by-product of IVF. If you are talking about, which we talked about earlier, that someone is going in for IVF and they're going to give away a couple of eggs to be used for research while they're having a child, they're not taking that risk for the purpose of research. They're taking that risk for the purpose of having a child, so that risk is not there for the research purpose.

Eggan: That's not correct because if they're taking that risk for their own fertility sake, then they shouldn't be taking it for research. Those two things we've already argued and discussed to be dissociated from one another.

Taylor: In terms of these analogies, risk is inversely proportional to cost. So I'm having trouble following this argument. So the liver donor gets nothing. The kidney donor gets nothing. The sperm donor gets $75 or something like that. The blood donor who has probably a slightly higher risk of injury than the sperm donor, which I would say is probably relatively minimal risk last time I thought about it, gets compensated to the tune of $30. Cost and risk clearly are either dissociated or inversely related.

Feit: I just don't think we should make this the issue. I think prop 71 is written and explains what CIRM is going to pay. It's going to pay expenses, and we can define what those are. They won't be unusual or incredible, like I will to go through Paris to get here or whatever that was. I think if we just stay with that I don't think we're going to solve it. If you go around the room, each of us has a moral, ethical attitude toward what we're talking about. I don't think you're really going to find a general consensus on this. I think our charge is written out already in prop 71 in terms of the reimbursement. I don't think we can change that. I think that by just sticking to that, we are making a statement that we're not going to be buying these things on the market. We're not going to put out an RFA to buy as many in the world market as we can. I think moving forward, there are plenty of steps that are being put in place, both in the grants procedures that we're setting forward, both in the regulations that we're setting forward and other working groups to protect the process of what we're trying to do. We've spoken for hours about protecting the donors, and we know what we want to do is we want to protect the individuals and move the research ahead.

Peters: Let me just follow that up by saying I think we can offer a distinction. What happens if someone off-site has a stem cell line available and those people compensated the women and that we can consider that to be a credible, ethical argument that they employed, and we could permit that to be used by CIRM researchers. How can we make that, then, consistent with what we're requiring of our own researchers? My suggestion is to say that we cannot use stem cell lines in which eggs or embryos were purchased, period. That would permit, then, compensation for the women donor. Those stem cell lines would be permitted.

Sheehy: If a fertility clinic supplies an embryo a researcher, what is that transaction?

Taylor: It the costs the IVF clinic whatever the shipping charge is.

Sheehy: So there's never an exchange on any of these.

Lo: Only for expenses. They can ask them to compensate for the fed ex charge or whatever, but they can't say beyond that we won't, $500.

Taylor: It's not really built into the payment schedule either. When these embryos were collected, nobody really was using them for this purpose. Going forward, maybe that will be calculated into the cost of the cycle.

Cibelli: You're making them a favor of just getting rid of those embryos.

Lo: You should pay us in addition. Maybe what we can do is try and have a briefing that lays out the discussion we have had and suggests some options for what we might want to say in regulations.

- What I'm hearing clearly is that we think consent is the key issue, and that that probably should come foremost, that

- there's a lot of sentiment here for allowing payment for expenses of the woman or gamete donor, and that we think that should be permissible for non-CIRM funded derivations, but that there's some discussion about having it totally open-ended payment. Ted has suggested language saying no buying or selling or payment, but expenses are allowed. Sometimes it's written as "reasonable expenses". I think if that is something that seems to work, we might try that.

[Public comment]

Reed: One, there are issues of sovereign nations. I don't think we can impose our standards on another country which has different ethical and religious backgrounds. I think one of the reasons that we put the no compensation in prop 71 was in a hopeful attempt to ease off some of the enemies of the research. It will not work. They're against it, they're going to stay against it until someone in their family gets sick and they get better because of the research after which they will become our biggest supporters.
There are charitable organizations which have backed off from supporting stem cell research because of religious pressures. So that's another kind of exploitation. I don't want to see us cut off from the rest of the world because of the fear of someone else's bad opinion of us. Those who do not support us do not support us, and the only thing that's going to change their minds is cure in their family. I really want us to be a part of the world community and not let anything block that.

Reynolds: Two regulatory regimes, I call them, are on my mind. And the first one is, of course, proposition 71, and it's always a little tricky to try to interpret the will of the voters. But not only is the language prohibiting compensation beyond reimbursement written into proposition 71 in a fairly clear way, although not entirely clear. That was among the ethical limitations written into proposition 71 that were part of the advertising campaign. And that's certainly contributed to the voters, who I would consider that part of your mandate here. That's not something to be revisited. I would tend to agree with Dr. Taylor, that this would be seen by the public, including your supporters, as a loophole that you're capitalizing on. A similar thing came up a little bit in terms of
returns to the state. It's in the law. It was part of the advertising that helped it pass, and I don't think that that's necessarily on the table. The other regime that's on my mind is the National Academies' recommendations. I suppose I'm a little bit concerned that in a couple of ways you're opening the door for lowering the floor a little bit below the national academies' recommendations. One way is the compensation issue. But going back earlier today, my interpretation of what's in the national academies is this thing about no limitations on downstream uses of the cells derived from the donors, that the national academies recommended guidelines explicitly recommend that that option be given to gamete donors, so I'd be a little concerned about creating multiple regulatory regimes that overlap in some ways, but not in all ways.

Eggan: I'd like to respond to both those points. Those are, first of all, that the National Academies of Science guidelines are just that, they're working guidelines. I think there needs to be recognition that they're works in progress, and that this is a rapidly emerging field. I think it's very important that a gamete donor be able to say I'm not comfortable with this downstream use of the cell line, and I think it's also important to say that it's just as reasonable for the scientists to turn around and say then I'm not comfortable with you participating in this research study. But I think there needs that sort of frank and open conversation between both the scientists and the donor, and that's what's going to prevent misunderstanding, and that's critical. I have to say, as I read the National Academies of Science Guidelines with respect to compensation, I believe that it's worded just that. And I think it's actually, if anything, probably left rather ambiguous with respect to what compensation means. I can't remember what the exact words are, but my understanding is that it's actually less restrictive in its choice of words than prop 71 is.

Lo: One of the things we'll ask staff to do in the interim before next meeting is to look very closely at the language of prop 71, the NAS guidelines, and other comparable statements about payment for research and provide some background. I want to switch gears and start thinking towards the future. I think this was a very useful meeting. I think we reached some important ideas about consent.

[Review of upcoming timetable of meetings, and APA regulatory process to develop and finalize the regulations]

I just want to say that the next meeting our goal is really to approve language on these proposed guidelines, final guidelines. Before then, staff is going to have a lot of work to do actually writing this out, translating it into regulatory language. I would suspect I would like to sort of be able to call on you either electronically or by telephone to try and push ahead on some of the issues that we haven't quite resolved, either to check and make sure the language seems right, but also there's some outstanding issues that, if we thought a little bit about ahead of time, it may facilitate our deliberations next meeting. Between now and January, we'd like to contact you either electronically and maybe by phone and to try and get some feedback from you as we sort of go about putting the ideas from the day into regulatory language.

Eggan: Maybe it's too late to change it, but is ten days a realistic amount of time for the staff to turn around everything we do in our meeting at the end of the month and get it to the hands of the ICOC for a reasonable review? We have a big job for those two days, and in turn, it will be a very big job to put the final regulations in the hands of the ICOC and for them to actually read it before they decide whether or not to approve it. I'm sort of sitting here wondering if that passes the red face test administratively.

Lo: We didn't approve anything today because we didn't have a quorum, but we need to have your approval of final language at the January meeting. So we need sort of have you approve before we leave if we're going to present it to the ICOC in February.

Prieto: I just want to remind people that these will still be interim regulations, and
Here's a long public comment period before these are cast in stone.

Hall: Just to keep our terminology straight, we now have interim regulations in place. These are draft regulations which we will, if approved by the ICOC, will then be submitted to or noticed with
OAL and then go out for public comment.

Hall: Correct me if I'm wrong here, but following public comment and our written response, then OAL decides whether we've made a major modification or a minor modification. If we made minor modifications, then they ask for 15 days of public response to reiterate. If they believe that we made a major change, then we have to go through once again the 45-day process of having public comment, written responses, and then we keep on that cycle till we get home. But if we were to make a major modification during that period, then we would be thrust back into starting over again. It is not the case that this will be a living document that we can continue to work on through this process. Once we submit it in February and it goes to OAL, then that's what -- that's our word on it.

Kiessling: because there were some problems with electronic information this time around, is it possible that when you send something to us, that you ask us to reply and make sure we got it because it didn't happen for a number of things this time. If you don't hear back from us, I think you should trigger it again.

Lomax: As a result, the past few weeks, we've had some concerns with e-mail, and we'll build a contingency in to make sure that isn't disruptive to the process.

The meeting was adjourned at 5:43pm